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## Clinical trial

# Clarithromycin versus doxycycline in the treatment of rosacea

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### Drug names

clarithromycin: Biaxin  
doxycycline: Vibramycin

Forty patients with rosacea were entered into a study comparing clarithromycin with doxycycline in the systemic treatment of mild and severe rosacea. The patients, 25 women and 15 men, aged from 26 to 62 years, were subdivided into two homogeneous groups with regard to age, sex, and disease severity. The first group of 23 patients, 14 women and 9 men, was treated with 250 mg of clarithromycin for 4 weeks twice daily, and then with 250 mg once daily for the following 4 weeks. The second group of 17 patients, 11 women and 6 men was treated with 100 mg of doxycycline for 4 weeks twice daily, and then with 100 mg once a day for the following 4 weeks. Both objective and subjective evaluations of the dermatosis were performed prior to therapy and after 4, 6, and 8 weeks of treatment.



## Objective evaluations

### Erythema

The erythema status was assessed by a colorimetric technique performed on color prints of the patients.<sup>1</sup> This system (Minolta Chromameter model CR 300, Osaka, Japan) enables the measurement of the skin color. Variations of erythema are represented by a single numerical value.<sup>1</sup>

### Telangiectases, papules, and pustules

The numbers and dimensions of telangiectases (TAE) were evaluated from the color prints and a score was assigned on the basis of the following scale: 0, no TAE; 1, less than five TAE located in the nasolabial sulcus and in the regio zygomatica; 2, 5–10 TAE located in the nasolabial sulcus and in the regio zygomatica; 3, between 10 and 20 confluent TAE; 4, 20–30 TAE, also diffused to the chin and forehead; 5, more than 30 TAE.

The numbers of papules and pustules were evaluated from the color prints and a score was assigned on the basis of the following scale: 0, no lesions; 1, less than 5 lesions; 2, 5–10 lesions; 3, 10–20 lesions; 4, 20–30 lesions; 5, more than 30 lesions.

## Subjective evaluations

Each patient was requested to express a subjective evaluation about the efficacy and tolerability of the treatment by assigning a score based on a scale ranging from 0 to 5. *Efficacy*: 0, no efficacy; 1, low efficacy; 2, traceable efficacy; 3, mild efficacy; 4, good efficacy; 5, high efficacy. *Tolerability*: 0, no side-effects; 1, occasional symptoms; 2, many symptoms; 3, mild side-effects; 4, severe side-effects; 5, very serious side-effects (inducing patients to discontinue the therapy).

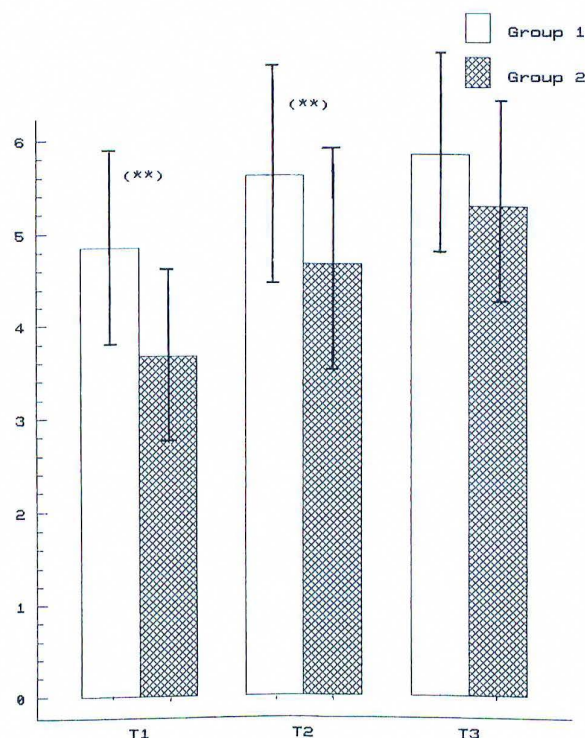
## Statistical methods

Statistical evaluation of the data collected from clarithromycin- and doxycycline-treated patients was performed by univariate and multivariate statistical analyses.

The mean values of the erythema index in the two groups of patients were compared by a Student's *t*-test, after 4 weeks (T<sub>1</sub>), 6 weeks (T<sub>2</sub>), and 8 weeks (T<sub>3</sub>) of therapy.

Nonparametric testing of the differences between the mean values of the other variables under examination (TAE, papules, pustules, efficacy, and tolerability) was carried out by a Mann-Whitney *U*-test.

The homogeneity of the two groups of patients was assessed by comparison, prior to treatment, of the mean



**Figure 1** Erythema. Mean values of  $\Delta E$  in clarithromycin- and doxycycline-treated groups of patients after 4, 6, and 8 weeks. At time T<sub>3</sub>, after 8 weeks of treatment, no significant difference was observed. Asterisks denote the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$ .

TAE values and papule and pustule variables (no significant difference was expected at T<sub>0</sub>).

In addition, a multivariate statistical analysis was performed. According to the discriminant function method, a new variable was calculated for each patient, as a linear combination of the values obtained for erythema, TAE, papules, and pustules. The mean values of this new variable in the two groups of patients were statistically compared at T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> by analysis of variance.

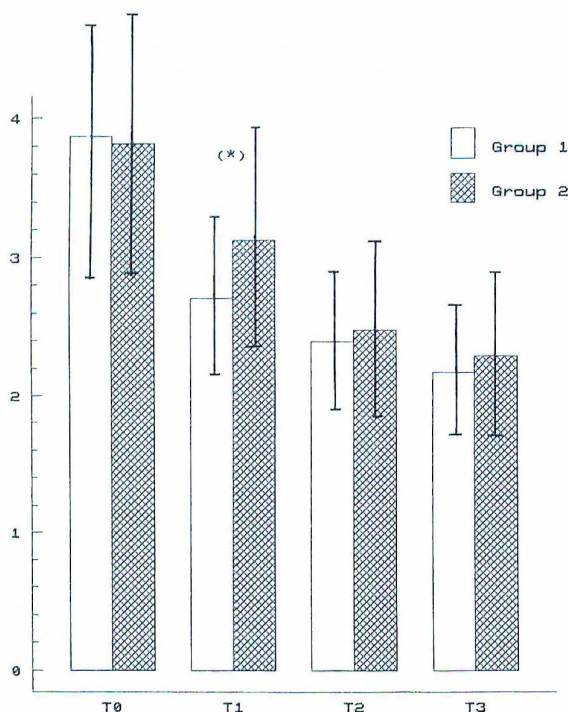
## Results

At the end of the treatment, the overall results provided evidence for a higher clarithromycin efficacy profile in comparison with doxycycline. The outcome assessment, based on the different parameters considered, revealed the following data.

### Objective evaluations

#### Erythema (Fig. 1)

Figure 1 shows the significant difference ( $P < 0.005$ ) between the mean values of the erythema index in the two



**Figure 2** Telangiectases (TAE). Mean values of TAE score in the two groups of patients at T<sub>0</sub> (before starting treatment), T<sub>1</sub> (4 weeks of treatment), T<sub>2</sub> (6 weeks of treatment), and T<sub>3</sub> (8 weeks of treatment). Asterisks represent the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$ . The homogeneity of the two groups is indicated by the lack of statistical significance at time T<sub>0</sub>

groups of patients observed after both 4 and 6 weeks of treatment (mean  $\pm$  standard error). At time T<sub>3</sub>, after 8 weeks of treatment, no significant difference was demonstrated.

#### Telangiectases (Fig. 2)

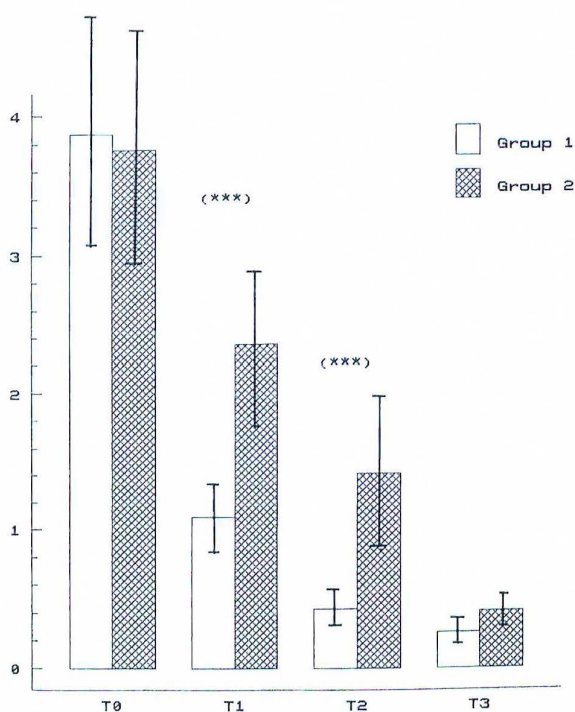
A significant difference ( $P < 0.05$ ) between the mean values of the specific score evaluating the numbers and dimensions of TAE in the two groups of patients was observed after 4 weeks of treatment. No significant differences were demonstrated at T<sub>2</sub> and T<sub>3</sub>.

#### Papules (Fig. 3)

A significantly faster decrease ( $P < 0.0005$ ) of the mean score evaluating the number of papules was assessed in the clarithromycin-treated patients, when compared with the doxycycline-treated patients, after 4 and 6 weeks of therapy. No significant differences were found at T<sub>3</sub>.

#### Pustules (Fig. 4)

The results obtained from a statistical comparison between the mean values of the score evaluating the number of



**Figure 3** Papules. Mean values of papule score in the two patient groups before starting treatment (T<sub>0</sub>) and after 4 weeks (T<sub>1</sub>), 6 weeks (T<sub>2</sub>), and 8 weeks (T<sub>3</sub>) of treatment. The homogeneity of the groups is indicated by the lack of statistical significance at time T<sub>0</sub>. Asterisks represent the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$

pustules were found to be strictly similar to those reported for the number of papules. A significant difference ( $P < 0.0005$ ) between the effects of the two regimens was assessed at times T<sub>1</sub> and T<sub>2</sub>. A comparison of the mean values observed at the end of therapy did not reveal a level of statistical significance.

#### Subjective evaluations

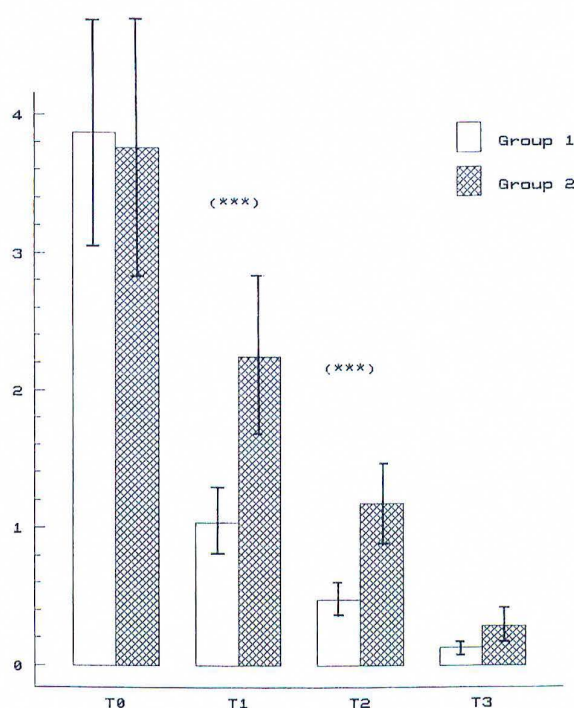
##### Efficacy (Fig. 5)

No statistically significant differences were observed in the two groups of patients at T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>.

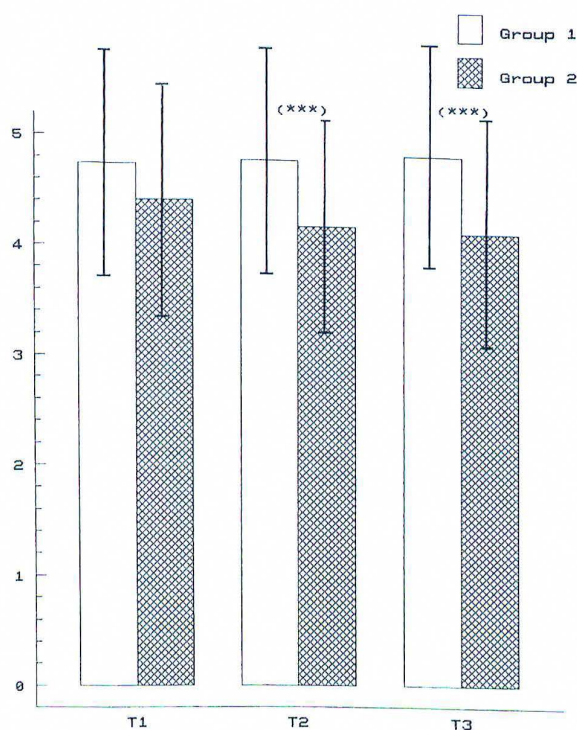
##### Tolerability (Fig. 6)

The total mean tolerability measured in Group 1 patients at the clarithromycin treatment rate used was equal to 0.32 (occasional side-effects). The total mean tolerability score measured in Group 2 patients at the doxycycline treatment rate used was equal to 1.06 (mild side-effects). A comparison of the mean values of the efficacy and tolerability





**Figure 4** Pustules. Mean values of pustule score in the two patient groups before treatment (T0), and after 4 weeks (T1), 6 weeks (T2), and 8 weeks (T3) of treatment. The homogeneity of the groups is indicated by the lack of statistical significance at T0. Asterisks denote the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$



**Figure 5** Efficacy. Mean values of treatment efficacy score. The score was assigned by both the patients of the clarithromycin-treated group and the doxycycline-treated group. Asterisks denote the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$

indices showed highly significant differences between the two groups of patients (Figs 5 and 6).

#### Discriminant function method

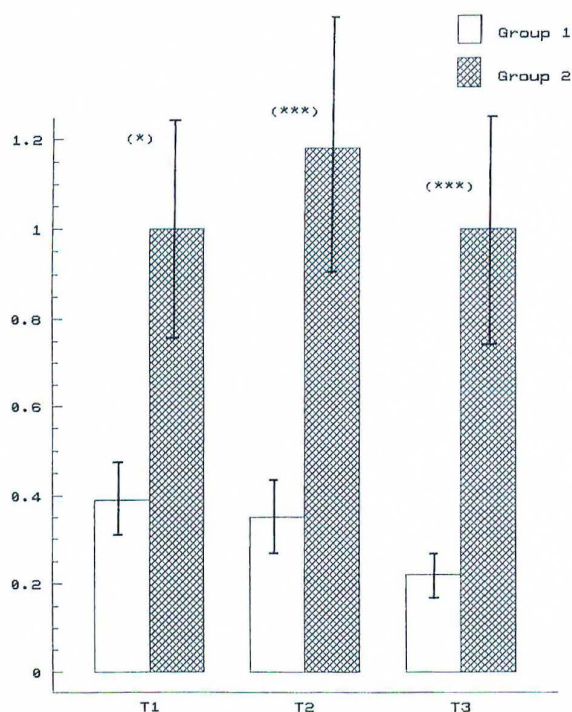
The final step of statistical analysis included the use of linear discriminant analysis as a multivariate approach. A comparison of the mean values of this new variable was then performed by analysis of variance. A highly significant difference was demonstrated at T1 and T2 ( $F=44.18$ ,  $P < 0.0005$ ). This further emphasizes the results provided by univariate analysis. More interestingly, a significant difference ( $F=5.3$ ,  $P < 0.005$ ) was also demonstrated at time T3, thus supporting a higher efficacy profile of clarithromycin versus doxycycline at the end of therapy. In addition, the faster improvement deriving from clarithromycin treatment was demonstrated by the fact that no statistical difference ( $F=0.81$ ,  $P < 0.05$ ) was observed in a comparison between the effects of doxycycline treatment at T3 with those of clarithromycin at T2. This analysis indicates that 6 weeks of clarithromycin treatment are equivalent to 8 weeks of doxycycline treatment.

#### Discussion

The etiology and pathogenesis of rosacea are still unknown. The systemic drugs first used in the treatment of rosacea were tetracyclines.<sup>2,3</sup> This was followed by the introduction of metronidazole.<sup>4</sup> Both therapies achieve significant improvements of dermatosis in 80% to 90% of cases,<sup>4,5</sup> and no statistically significant differences were observed between them.<sup>5</sup>

The pharmacologic mechanisms of action of both metronidazole and tetracyclines have been widely investigated. The therapeutic activity of tetracyclines seems to be related to their anti-inflammatory efficacy.<sup>6</sup>

Clarithromycin, a recently synthesized macrolide, has been proven to be able to penetrate into phagocytes *in vitro*.<sup>7</sup> The present study reveals that clarithromycin is a powerful tool in the treatment of rosacea. It yields improvements which are significantly more consistent when compared with those obtained with doxycycline. In contrast with tetracyclines and metronidazole, clarithromycin is a very safe therapy inducing only occasional and slight side-



**Figure 6** Tolerability. Mean values of tolerability score of the two regimens. The score was subjectively assigned by the two groups of patients. Asterisks denote the level of statistical significance: \* $P < 0.05$ ; \*\* $P < 0.005$ ; \*\*\* $P < 0.0005$

effects. This significantly increases patient compliance and is of particular interest when considering the long-term therapy required. The mechanism of action of the drug in dermatosis has not yet been established. It is conceivable that clarithromycin also has anti-inflammatory capabilities.

Rebora *et al.*<sup>8</sup> recently found *Helicobacter pylori* in the gastric juices of 84% of 31 patients suffering from rosacea. They suggested an etiologic relationship between rosacea and *Helicobacter pylori* infections on the basis of the

correlation between clinical improvement and abatement of the *Helicobacter pylori* isolates and serology after treatment with metronidazole.<sup>9</sup> Because clarithromycin is effective against *Helicobacter pylori*, this could explain the efficacy of this macrolide in the treatment of rosacea.<sup>10</sup>

Further studies will yield new insights into the pharmacologic mechanisms of action of clarithromycin in the treatment of rosacea.

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