*The Journal of Laryngology & Otology (2014)*, ***128***, *591–598*.

doi:10.1017/S0022215114001157

**MAIN ARTICLE**

# Ciprofloxacin plus fluocinolone acetonide versus ciprofloxacin alone in the treatment of diffuse otitis externa

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## Abstract

*Objective*: We aimed to evaluate the clinical efficacy of ciprofloxacin plus fluocinolone acetonide (antibiotic plus corticosteroid) ear drops compared to ciprofloxacin (antibiotic) ear drops in diffuse otitis externa.

*Methods*: This was a multicentre, randomised, parallel-group, double-blind study involving 590 patients of both sexes aged 7 years or older.

*Results*: The rate of clinical cure was higher ($p = 0.01$) with ciprofloxacin plus fluocinolone acetonide than with ciprofloxacin alone. The mean total symptom score was lower with ciprofloxacin plus fluocinolone acetonide ($p = 0.005$). No differences were found in the percentage of patients reporting resolution of otalgia between patients receiving ciprofloxacin plus fluocinolone acetonide and patients receiving only ciprofloxacin. Resolution of oedema and otorrhoea ($p = 0.003$ and $p = 0.002$, respectively) was higher with ciprofloxacin plus fluocinolone acetonide, as was eradication or presumed eradication ($p = 0.003$). There were eight mild adverse events, three with the ciprofloxacin plus fluocinolone acetonide combination (not related to the treatment) and five when ciprofloxacin was administered alone (directly related to the treatment).

*Conclusions*: Ciprofloxacin plus fluocinolone acetonide is a more effective treatment for diffuse otitis externa than ciprofloxacin alone. The ciprofloxacin plus fluocinolone acetonide combination also has an excellent safety profile.

**Key words:** Ear, External; Fluocinolone Acetonide; Ciprofloxacin; Administration, Topical

## Introduction

Infectious processes of the external ear often result from the action of certain bacteria found on the epithelium of the external auditory canal. Diffuse otitis externa is the result of a bacterial infection that manifests itself as an acute dermo-epidermitis of the external auditory canal. The most common infectious agent involved in its aetiology is *Pseudomonas aeruginosa*.[1]

From a clinical point of view, the symptomatology can begin as a pruritus that intensifies progressively to the point where it becomes full-blown otalgia. This is accompanied by oedema of the external auditory canal, which causes a stenosis that can vary in intensity, giving rise to a sensation of the ear being covered or even of slight hearing loss. Otological examination shows a moderate, watery or slightly purulent secretion that grows in proportion to a significant increase in otalgia, as well as a positive tragus test.

Even though in most cases the symptomatology evolves spontaneously towards healing, in some cases the infection, or the inflammatory reaction phenomena, can extend to the soft periauricular tissue, resulting in perichondritis of the auricular pavilion. The intensity of the otalgia and the possibility of complications make medical treatment advisable, despite the difficulties that the treatment of ear infections frequently presents. The systemic administration of antibiotics can mean that concentrations in the ear tissue are too low, thereby compromising drug efficacy. Additionally, some infectious micro-organisms are highly resistant to the most commonly used antibiotics for this pathology. These circumstances make it advisable to administer the antibiotic topically since, by using this method, ear tissue concentrations reach effective levels without the inherent risks found with systemic administration. Antibiotics with a high activity against the micro-organisms most frequently involved in the aetiology of these infections should be used.

One of the standard treatments for ear infections up to now has been the topical administration

Accepted for publication 21 July 2013 First published online 7 July 2014

of aminoglycosides,[2–14] especially gentamicin.[5,6] Gentamicin ototoxicity and nephrotoxicity are well known.[2–4,15] Gentamicin can cause auditory and vestibular problems on reaching the inner ear.[9,10] Reduced bactericidal effect against *Pseudomonas* and Enterobacteriaceae has also been observed.[7,16]

Ciprofloxacin is a second-generation fluoroquinolone antibiotic. It acts as an inhibitor of bacterial topoisomerase II (DNA gyrase) and its homologue topoisomerase IV, enzymes that are required for bacterial DNA replication, and has *in vitro* activity against a wide range of Gram-negative and Gram-positive bacteria.[15–18]

Ciprofloxacin is an active antibiotic against the majority of micro-organisms that cause ear infections (essentially, *P aeruginosa*, *Staphylococcus aureus* and *S epidermidis*, as well as the majority of the Enterobacteriaceae family of bacteria). Different trials have shown that ciprofloxacin, unlike aminoglycosides, does not show ototoxicity at the cochleovestibular level.[19–22] In addition, different studies have established the efficacy of ciprofloxacin when administered orally.[8–14] However, the need to administer high doses to achieve acceptable tissue concentrations, with the consequent possibility of side effects and high costs, have led investigators to the idea of applying ciprofloxacin to the ear topically.

Various trials have shown excellent results for the treatment of ear infections with ciprofloxacin when applied topically.[1,19–25] In one trial,[21] carried out on ear infections caused by *P aeruginosa*, better results were achieved with the topical application of ciprofloxacin than with gentamicin administered systemically (87 and 66 per cent, respectively). In other trials, the non-ototoxicity of ciprofloxacin was shown after the repeated bilateral application of ear drops, showing clinical efficacy in 95 per cent of cases.[19,25]

In a trial carried out on patients with ear infections, García Rodríguez *et al*. showed that clinical and microbiological efficacy was higher when ciprofloxacin was administered topically (95.2 per cent), than when it was administered orally (68.2 per cent).[1]

The safety of ciprofloxacin has been evaluated in numerous trials involving patients treated with ciprofloxacin ear drops,[26,27] where plasma levels were measured by high-resolution liquid chromatography. The results of these findings, with a detection limit of 5 ng/ml, were negative, indicating that the antibiotic was not absorbed systemically following topical administration.

In this context, the addition of a corticosteroid with proven safety and efficacy, such as fluocinolone acetonide, is fully justified in the treatment of disease processes with a significant inflammatory component, such as acute otitis externa. Different pre-clinical trials on the association of ciprofloxacin and fluocinolone acetonide, including one investigating dermal sensitivity and subacute (30 days) ototoxicity in guinea pigs,[3] have not shown irritability or ototoxicity, either at the functional or morphological level.

Another multicentre, double-blind clinical trial compared the efficacy and tolerability of ciprofloxacin plus fluocinolone acetonide *vs* a combination of polymyxin B, neomycin and fluocinolone acetonide in the treatment of diffuse otitis externa. Of the 206 patients included in the trial, 177 were evaluated for treatment efficacy; the combination of ciprofloxacin and fluocinolone acetonide was more effective by 4.6 per cent than the polymyxin B, neomycin and fluocinolone acetonide combination (P Quesada, unpublished data). Considering the results of this trial, and those published in the New Drug Application 20–805 of the US Food and Drug Administration for ciprofloxacin and hydrocortisone obtained by the Bayer Corporation,[28] we deemed it necessary to conduct a comparative clinical efficacy trial between ciprofloxacin plus fluocinolone acetonide ear drops and ciprofloxacin ear drops, to demonstrate the benefits of combining a corticosteroid with an antibiotic in the treatment of diffuse otitis externa.

## Materials and methods

### *Study design and patient selection*

This was a multicentre, randomised, parallel-group, double-blind clinical trial involving 590 patients from 20 centres. The trial included patients of both sexes aged seven years or older, with a diagnosis of diffuse otitis externa, who could follow trial instructions and who gave written consent to participate in the study. In the case of minors and patients with disabilities, written consent was given by their legal representative. For minors of 12 years or older, the subject also gave their consent to participate in the trial, having been provided with all the pertinent information in a manner they could understand.

Exclusion criteria included: a diagnosis different to diffuse otitis externa; possible otomycosis; presence of mastoiditis requiring surgery or having been operated on within the last six months; present or suspected infection requiring systemic antibiotic treatment; diseases or structural anomalies impeding therapeutic response evaluation.

Patients were divided into two groups, the treatment group receiving 4–6 ear drops of the combination of ciprofloxacin 0.3 per cent and fluocinolone acetonide 0.025 per cent every 8 hours for 8 days, and the control group receiving 4–6 ear drops of ciprofloxacin 0.3 per cent every 8 hours for 8 days.

The primary objective was to verify the clinical efficacy of the topical treatment of diffuse otitis externa with ear drops containing a combination of ciprofloxacin and fluocinolone acetonide. The secondary objective was to evaluate the reduction in and end of the parameters 'hours with pain' and 'intensity of pain' using ciprofloxacin plus fluocinolone acetonide compared to ciprofloxacin alone. Safety was evaluated by recording any adverse events.

https://doi.org/10.1017/S0022215114001157 Published online by Cambridge University Press

The study was carried out according to the guidelines on good clinical practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the provisions of the Declaration of Helsinki (as revised in Seoul in 2008).[29] The study was approved by the Clinical Research Ethics Committee of Vall d'Hebron Hospital, Barcelona, Spain. The study complied with Organic Law 15/1999 on the Protection of Personal Data concerning the confidentiality of patients' data.

*Study variables*

The clinical efficacy parameters included overall clinical outcome, sign/symptom score and total symptom score for pain (otalgia), oedema and otorrhoea, evaluated at the beginning of treatment and after 8 days. The overall clinical outcome was categorised into clinical cure (i.e. the scores for pain, oedema and otorrhoea were 0) and clinical failure (any symptom score different from 0 or missing at the end of treatment). The sign/symptom score was assessed by means of a visual analogue scale (VAS) ranging from 0 to 10. Each sign/symptom was scored as severe (or 3) if the VAS score was 7–10, moderate (or 2) if the VAS score was 3,5–7, mild (or 1) if the VAS score was 0–3,5 or absent (or 0) if the VAS score was 0. The total symptom score was the sum of the three sign/symptom scores, ranging from 0 to 9.

Assessment of the bacteriological response to therapy was performed by the investigators, who compared the smears and cultures taken on the first day (prior to treatment) and on the last day of treatment. Bacteriological response was rated as: eradication (the micro-organism responsible for the infection was absent at the end of the treatment); presumed eradication (absence of secretions from which to make cultures; clinical cure observed); persistence (the micro-organism responsible for the infection was present at the end of the treatment); undetermined response (the bacteriological response could not be evaluated for a reason not previously mentioned, e.g. a post-treatment culture could not be taken); and superinfection (a new micro-organism was responsible for the infection; it required specific treatment and appeared at any time during the treatment period or up to 4 days after the end of the trial).

Clinical efficacy was also evaluated by the investigators' subjective impression of clinical efficacy, the amount of rescue medication (paracetamol) taken by patients in each treatment group and the reduction in and end of the parameters 'hours with pain' and 'intensity of pain' in both treatments. Safety was evaluated by recording any adverse events.

All clinical data were recorded in a case record form specifically designed for the trial. The trial lasted 8 days (valid treatment interval: 7–10 days) for each patient, including two visits (one at baseline and the other at the end of treatment).

*Statistical analysis*

Descriptive statistics were performed for all the analysed variables. Two-sided 95 per cent confidence intervals (CIs) for the difference between treatment groups in the proportion of patients experiencing an outcome were used to test the hypothesis that ciprofloxacin plus fluocinolone acetonide is more effective than ciprofloxacin administered alone. Superior effectiveness for the primary end point was declared if the 95 per cent CI of the difference between treatments excluded zero. Each sign/symptom score and total symptom score were recorded both at the baseline and end-of-treatment visits, as well as any changes between the two visits. The total symptom score was analysed between treatments during each visit by using the Mann–Whitney U and Wilcoxon signed rank tests. Qualitative data were analysed using the chi-square test.

The reduction in and end of the 'intensity of pain' and 'hours of pain' parameters was verified by analysing survival curves and using the log-rank test, determining the median 'hours with pain' for each treatment. The comparative exploratory values of the rescue medication in both treatment groups were also evaluated.

The analysis of adverse events and withdrawal from treatment, including their frequencies, was of a descriptive nature. All data were analysed using the SAS statistical software package (version 6.12; SAS Institute Inc., Cary, North Carolina, USA).

## Results

*Demographic and clinical data*

Of the 590 patients, 296 were assigned to receive treatment with ciprofloxacin plus fluocinolone acetonide ear drops, while the other 294 patients were assigned to receive only ciprofloxacin ear drops. There were 45 withdrawals, 23 (7.8 per cent) from the ciprofloxacin plus fluocinolone acetonide group (16 lost to follow up, 4 to treatment inefficacy, 2 to adverse events and 1 due to non-compliance with the treatment plan), and 22 (7.5 per cent) from the ciprofloxacin group (18 lost to follow up, 2 due to treatment inefficacy, 1 to an adverse event and 1 due to non-compliance with the treatment plan).

In the ciprofloxacin plus fluocinolone acetonide group, there were 154 males (52.0 per cent) and 142 females (48.0 per cent) with a mean age of 41.9 ± 17.8 years (± standard deviation (SD)); in the ciprofloxacin group, there were 160 males (54.4 per cent) and 134 females (45.6 per cent), with a mean age of 43.7 ± 17.3 years (± SD). Prior history of otitis was present in 106 patients (35.9 per cent) from the ciprofloxacin plus fluocinolone acetonide group and 116 patients (39.5 per cent) from the ciprofloxacin group.

A treatment for otitis prior to inclusion in the trial was given to 74 (25.0 per cent) patients from the ciprofloxacin plus fluocinolone acetonide group and to 78

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(26.5 per cent) patients from the ciprofloxacin group. The time interval since the last treatment was 12.3 ± 17.3 days in the ciprofloxacin plus fluocinolone acetonide group and 17.9 ± 25.2 days in the ciprofloxacin group.

Among the patients from the ciprofloxacin plus fluocinolone acetonide group, 149 (50.3 per cent) suffered from right-sided otitis, 114 (38.5 per cent) from left-sided otitis and 33 (11.1 per cent) from bilateral otitis. In the ciprofloxacin group, 135 (45.9 per cent) patients had right-sided otitis, 114 (38.8 per cent) had left-sided otitis and 45 (15.3 per cent) had bilateral otitis.

*Efficacy outcomes*

The most frequent symptoms found at baseline among patients with otitis were otalgia (98 per cent for the ciprofloxacin plus fluocinolone acetonide group compared to 98.6 per cent for the ciprofloxacin group), otorrhoea (80.4 per cent for the ciprofloxacin plus fluocinolone acetonide group compared to 85.4 per cent for the ciprofloxacin group), oedema (74.7 per cent for the ciprofloxacin plus fluocinolone acetonide group compared to 75.5 per cent for the ciprofloxacin group) and hypoacusis (70.6 per cent for the ciprofloxacin plus fluocinolone acetonide group compared to 69.4 per cent for the ciprofloxacin group).

Clinical efficacy at the end of treatment was significantly better with ciprofloxacin plus fluocinolone acetonide than with ciprofloxacin alone (Figure 1). The rate of clinical cure was 79.7 per cent in patients receiving ciprofloxacin plus fluocinolone acetonide and 70.8 per cent in patients receiving only ciprofloxacin, with $p = 0.01$ and the 95 per cent CI (bilateral) for the difference between two proportions (9.0 per cent) ranging from 2.1 to 15.9 per cent in favour of ciprofloxacin plus fluocinolone acetonide. Clinical failure was 20.3 per cent for ciprofloxacin plus fluocinolone acetonide and 29.3 per cent for ciprofloxacin alone. Because the 95 per cent CI of the difference between treatments excluded zero, the ciprofloxacin plus fluocinolone acetonide combination was found to be more effective than ciprofloxacin administered alone.

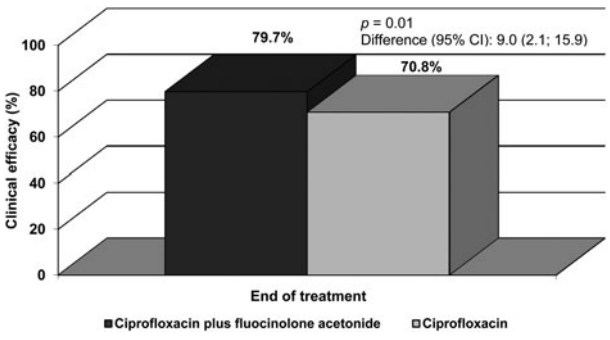


FIG. 1

Clinical efficacy at the end of treatment achieved with ciprofloxacin plus fluocinolone acetonide compared to ciprofloxacin used alone. CI = confidence interval

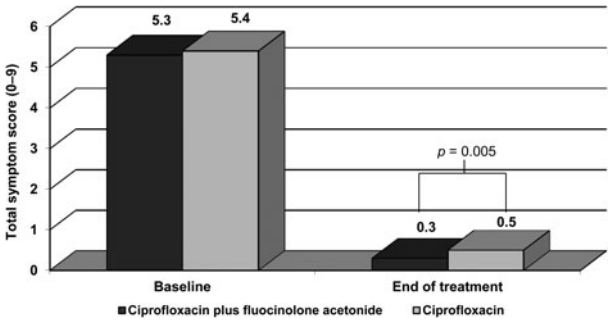


FIG. 2

Total symptom score with ciprofloxacin and fluocinolone acetonide compared to ciprofloxacin used alone.

Total symptom score was reduced at the end of treatment with both treatments, however, it was significantly lower in patients taking ciprofloxacin plus fluocinolone acetonide than in patients taking only ciprofloxacin (Figure 2). At the end of treatment, patients receiving ciprofloxacin plus fluocinolone acetonide had a mean (SD) total symptom score of 0.3 (0.9). The mean (SD) total symptom score for patients receiving only ciprofloxacin was 0.5 (1.1), the difference being significantly lower ($p = 0.005$) with ciprofloxacin plus fluocinolone acetonide.

Otalgia, oedema and otorrhoea were resolved in a high percentage of patients at the end of the trial with both treatments (Figure 3). No differences were found in the percentage of patients reporting resolution of otalgia between patients receiving ciprofloxacin plus fluocinolone acetonide (88.2 per cent) and patients receiving only ciprofloxacin (86.1 per cent).

Oedema resolution was significantly higher in patients receiving ciprofloxacin plus fluocinolone acetonide than in patients receiving only ciprofloxacin (84.8 per cent compared to 75.2 per cent, respectively; $p = 0.003$), and the 95 per cent CI for the difference between two proportions (9.6 per cent) ranged from 3.2 to 16.0 per cent in favour of ciprofloxacin plus fluocinolone acetonide.

There was also a significantly higher proportion of patients with resolution of otorrhoea between patients receiving ciprofloxacin plus fluocinolone acetonide and patients receiving only ciprofloxacin (87.5 compared to 77.9 per cent, $p = 0.002$), and the 95 per cent CI for the difference between two proportions (9.6 per cent) ranged from 3.6 to 15.7 per cent in favour of ciprofloxacin plus fluocinolone acetonide.

The intensity of symptoms was reduced at the end of the trial with both treatments, the reduction in intensity for oedema and otorrhoea being significantly greater ($p < 0.05$) for ciprofloxacin plus fluocinolone acetonide. The mean intensity of oedema decreased from 5.1 to 0.2 with ciprofloxacin plus fluocinolone acetonide, and from 5.2 to 0.3 with ciprofloxacin alone, being significantly different ($p = 0.002$) at the end of treatment in favour of ciprofloxacin plus fluocinolone acetonide. The mean intensity of otorrhoea decreased

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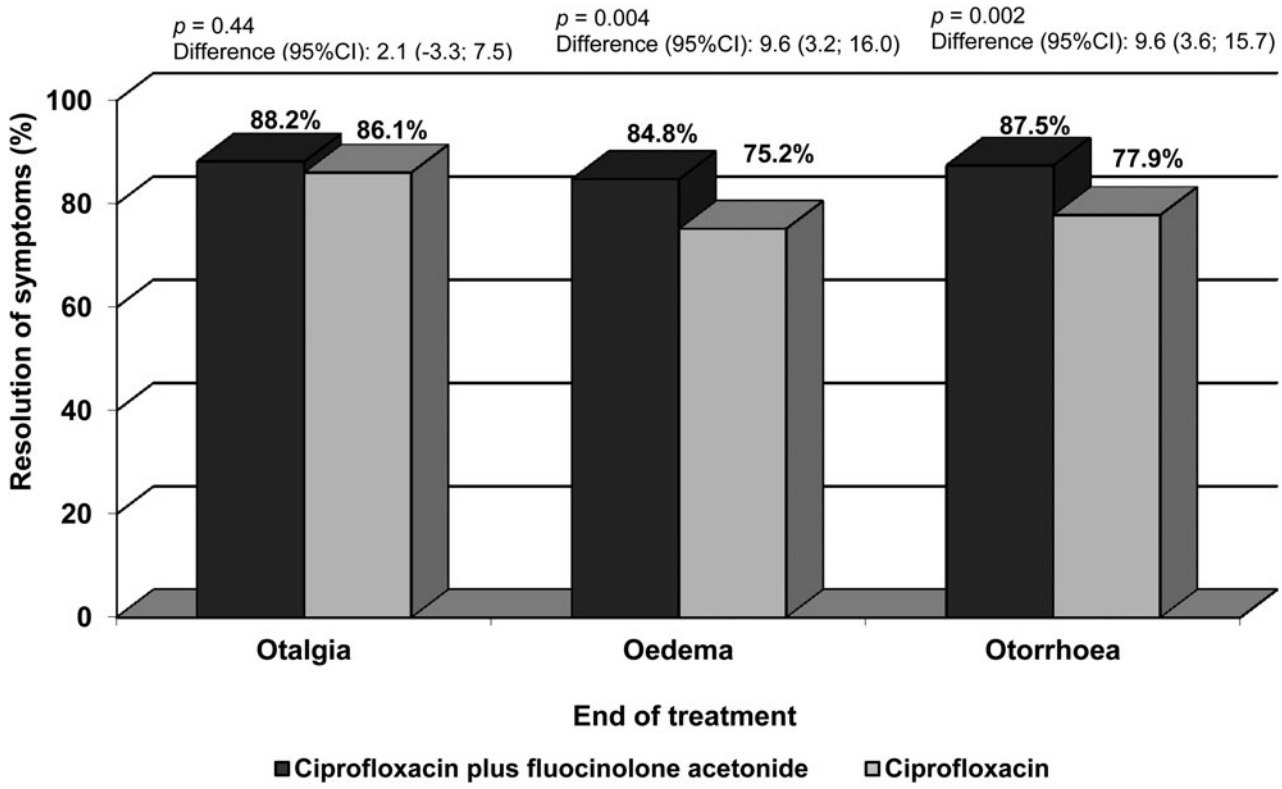


FIG. 3

Resolution of otalgia, oedema and otorrhoea with ciprofloxacin and fluocinolone acetonide compared to ciprofloxacin used alone. CI = confidence interval

from 4.1 to 0.2 with ciprofloxacin plus fluocinolone acetonide, and from 4.1 to 0.5 with ciprofloxacin alone, being significantly different ($p = 0.0005$) at the end of treatment in favour of ciprofloxacin plus fluocinolone acetonide.

Significant differences were found between ciprofloxacin plus fluocinolone acetonide and ciprofloxacin administered alone in the percentage of patients with symptoms of otorrhoea (4.4 *vs* 11.2 per cent; $p = 0.001$) and hypoacusis (9.8 *vs* 15.6 per cent; $p = 0.02$) at the end of treatment.

Differences were also observed in the bacteriological response to the two study treatments in favour of ciprofloxacin plus fluocinolone acetonide (Figure 4). Eighty-nine point two per cent of patients treated with ciprofloxacin plus fluocinolone acetonide and 82.3 per cent of patients treated with ciprofloxacin alone showed eradication or presumed eradication of the agent causing the otitis ($p = 0.01$).

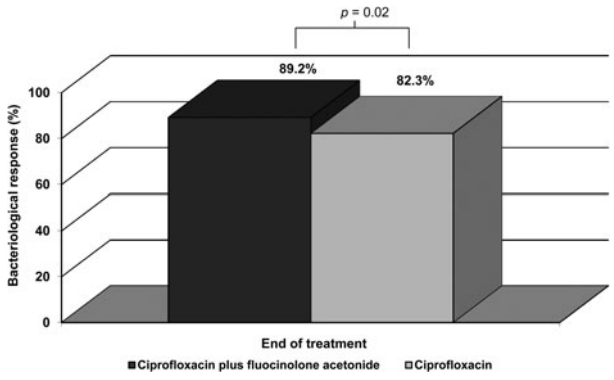


FIG. 4

Bacteriological response to treatment with ciprofloxacin and fluocinolone acetonide compared to ciprofloxacin used alone.

No significant differences were observed between the treatments with regards to the duration of pain. The mean value of this secondary efficacy end point was 72.2 ± 49.1 hours (ciprofloxacin plus fluocinolone acetonide) and 72.6 ± 46.0 hours (ciprofloxacin). The percentage of patients without pain after the treatment was high (94.8 per cent), being slightly higher with ciprofloxacin plus fluocinolone acetonide, although the differences observed were not statistically significant.

Rescue medication was administered to 69.3 per cent of patients treated with ciprofloxacin plus fluocinolone acetonide and 74.4 per cent of patients treated with ciprofloxacin only, with an average number of capsules of paracetamol of 5.7 ± 5.9 and 6.2 ± 6.3, respectively, for ciprofloxacin plus fluocinolone acetonide and ciprofloxacin alone. No significant differences were found between the two treatments even though more rescue medication was administered to patients treated only with ciprofloxacin.

The subjective impression of clinical efficacy by the investigators tended to be more favourable for ciprofloxacin plus fluocinolone acetonide than for ciprofloxacin alone, even though the differences were

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not significant. The cure rates evaluated by the investigators were 86.8 (ciprofloxacin plus fluocinolone acetonide) and 81.3 per cent (ciprofloxacin), respectively.

The two treatments showed a favourable safety profile. There were only eight adverse events in the trial, and none was serious. None of the adverse events observed with ciprofloxacin plus fluocinolone acetonide, and only two of the adverse events observed with ciprofloxacin were considered to be related to the treatment. Only one patient was hospitalised due to an adverse event, which was not related to the treatments. Eighteen (6.1 per cent) of the 296 patients randomised in the ciprofloxacin plus fluocinolone acetonide group and 20 (6.8 per cent) of the patients randomised in the ciprofloxacin group withdrew prematurely from the trial; three patients from the ciprofloxacin plus fluocinolone acetonide group and two patients from the ciprofloxacin group withdrew due to the 'treatment inefficacy'. This good safety profile helped to promote a high rate of treatment compliance, which was 85.0 per cent for ciprofloxacin plus fluocinolone acetonide and 84.3 per cent for ciprofloxacin.

## Discussion

Ciprofloxacin is a broad-spectrum antibiotic with proven efficacy against micro-organisms present in ear infections.[30–36] Ciprofloxacin's ability to target micro-organisms in an anatomical zone with restricted access, such as the external auditory canal in cases of diffuse otitis externa, can be further increased by the additional administration of anti-inflammatories, such as corticosteroids.[37] As with other corticosteroids, fluocinolone acetonide reduces membrane permeability, induces vasoconstriction, reduces vascular permeability and serum extravasation, thereby reducing inflammation, and allows ear drops to reach the focus of the infection, in the external auditory canal, with greater ease. The principal aim of this study was to evaluate the clinical efficacy of ciprofloxacin plus fluocinolone acetonide compared to ciprofloxacin administered alone when treating diffuse otitis externa.

The combination of ciprofloxacin plus fluocinolone acetonide showed superior clinical efficacy, defined as clinical cure, than ciprofloxacin administered alone in the treatment of diffuse otitis externa. Thus, clinical cure reached 79.7 per cent for ciprofloxacin plus fluocinolone acetonide and 70.8 per cent for ciprofloxacin alone. These results are within the range of clinical cure rates found in another trial comparing ciprofloxacin with tobramycin and topical otic powder, with cure rates of 77, 56 and 86 per cent, respectively.[38]

Furthermore, similar results were recorded in a meta-analysis of 18 clinical trials, which showed that clinical cure rates of 65–80 per cent were obtained with topical anti-microbial therapy in acute otitis externa.[39] Although the meta-analysis results suggested minimal or no difference in clinical or bacteriological cure rates among topical agents, some of the more recent studies have shown significant differences in the rapidity of treatment response or symptom resolution. For example, the addition of dexamethasone to ciprofloxacin reduced median ear pain from 4.7 to 3.8 days.[40]

In our study, the mean duration of pain did not differ between ciprofloxacin administered alone and ciprofloxacin plus fluocinolone acetonide (72.6 *vs* 72.2 hours, respectively), the mean duration of pain being 3 days in both cases, which is lower than the 3.8 days with ciprofloxacin and dexamethasone.

The bacteriological response was slightly better with ciprofloxacin plus fluocinolone acetonide than with ciprofloxacin alone (cases of eradication or presumed eradication: 89.2 *vs* 82.3 per cent, $p = 0.02$). These results are similar to the microbiological eradication rates found in two other trials with ciprofloxacin plus dexamethasone, which were 86 and 92 per cent *vs* 84 and 89 per cent for a combination of polymyxin B, neomycin sulphate and hydrocortisone.[36,41]

A recent systematic review of 14 randomised controlled studies in acute otitis externa, 8 of them using ciprofloxacin 0.2 and 0.3 per cent solutions, demonstrated the non-inferiority of ciprofloxacin in the treatment of otitis externa, in terms of cure rate and microbiological eradication, compared to a combination of polymyxin B, neomycin sulphate and hydrocortisone.[41]

- **The combination of ciprofloxacin and fluocinolone acetonide, administered as 4–6 ear drops every 8 hours for 8 days, is an effective treatment against diffuse otitis externa**
- **Our trial showed that the combination of antibiotic (ciprofloxacin) and corticosteroid (fluocinolone acetonide) is more effective than ciprofloxacin used alone**
- **Both treatments have an excellent safety profile, with adverse events being low in both treatments**

The intensity of otalgia, oedema and otorrhoea, the most frequent symptoms in the patient population affected by diffuse otitis externa included in our trial, decreased further with ciprofloxacin plus fluocinolone acetonide than with ciprofloxacin alone. Both treatments in the trial induced a reduction in the pain experienced by patients, which is reflected as much in the time it takes for pain to disappear as in the percentage of patients without pain after the conclusion of treatment.

The safety results obtained in this trial do not show significant differences between the two treatments. Clinical compliance was similar in both treatments. The number of withdrawals and dropouts observed with both treatments during the trial was low (7.8 per cent of the patients treated with ciprofloxacin plus

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fluocinolone acetonide and 7.5 per cent of the patients treated with ciprofloxacin), and only three patients in the ciprofloxacin plus fluocinolone acetonide group and two in the ciprofloxacin group abandoned the trial due to treatment inefficacy.

The number of adverse events observed was low (three or 1.0 per cent with ciprofloxacin plus fluocinolone acetonide and five or 1.7 per cent with ciprofloxacin alone) and none of these adverse events were serious, which confirms the high tolerability of the ciprofloxacin plus fluocinolone acetonide combination and of ciprofloxacin used alone and the absence of ototoxicity in both treatments. The low rate of adverse events described for ciprofloxacin was also confirmed in the previously mentioned systematic review, including eight studies with ciprofloxacin where the low rate of side effects and the good safety profile were highlighted.[41]

In conclusion, the combination of an antibiotic (ciprofloxacin) with a corticosteroid (fluocinolone acetonide) constitutes a safe and effective treatment for diffuse otitis externa. The combination of two substances that act in different ways, such as the anti-inflammatory effects of fluocinolone acetonide and the antibiotic action of ciprofloxacin, allow for superior levels of clinical efficacy and bacteriological response to those obtained by administering only ciprofloxacin.

## Acknowledgements

This study was supported in part by a grant from Laboratorios SALVAT S.A.

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Dr J L Guerrero takes responsibility for the integrity of the content of the paper
Competing interests: This study was supported in part by a grant from Laboratorios SALVAT S.A.