Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The present study compared topically applied clobetasol propionate ointment and ciclosporin for the palliative care of symptomatic, atrophic and erosive, oral lichen planus (OLP). Both drugs were mixed separately with 4% hydroxyethyl cellulose gel to obtain a final concentration of 0.025% for clobetasol and 1.5% for ciclosporin. Antimycotic prophylaxis was added to the therapy of both treatment groups as prophylaxis against oropharyngeal candidosis. The antimycotic prophylaxis consisted of miconazole gel and a 0.12% chlorhexidine mouth rinse.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Consecutive patients attending the hospital were enrolled. The inclusion criteria were the presence of painful lesions and clinical and histological diagnosis of atrophic or erosive OLP on the basis of World Health Organization criteria. Exclusion criteria were specified, such as the presence of histological signs of dysplasia, the use of lichenoid reaction-inducing drugs, the presence of amalgam fillings close to lesions, and therapy for OLP in the 6 months prior to the study. Further exclusion criteria were skin, genital or other extraoral lesions, and pregnant or breastfeeding women.

Setting
The setting was tertiary care. The economic study was carried out in Turin, Italy.

Dates to which data relate
The effectiveness evidence and resource used referred to the period 1999 to 2002. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
It seems that the costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The sample size was calculated according to published data. Overall, 40 patients were enrolled in the study, 20 being
allocated to each group. In the clobetasol group, the mean age was 67.95 (+/- 7.93) years and the male-to-female ratio was 5:14 (one patient did not complete the study because she did not return for her review appointments). In the ciclosporin group, the mean age was 63.40 (+/- 9.59) years and the male-to-female ratio was 9:11.

**Study design**
The study was a prospective, randomised, controlled double-blind study that was conducted in a single centre. The study was divided into two phases. Phase I consisted of the assigned topical treatment for 2 months, while Phase II was a 2-month follow-up period without therapy. Randomisation was performed using computer-generated random number tables. Each patient was examined at the beginning of therapy, and then every 2 weeks during the 2 months of treatment and the 2 months of follow-up.

**Analysis of effectiveness**
It was not reported whether the analysis was conducted on an intention to treat basis or on treatment completers only. The clinical data were scored according to medical literature. The scale assigned a score of 0 for no lesions, 1 for hyperkeratotic lesions, 2 for atrophic area <1 cm2, 3 for atrophic area >1 cm2, 4 for erosive area <1 cm2, and 5 for erosive area >1 cm2. The symptomatology score was obtained using a visual analogue scale marked from no pain to most severe pain experienced. Complete resolution of the clinical signs (complete response) was defined as the disappearance of all atrophic or erosive lesions, regardless of any persistent hyperkeratotic lesions. Complete resolution of the symptoms (no symptoms) was defined as the absence of any discomfort. The numerical difference between baseline and end point scores expressed the clinical and symptomatic improvement. There were no significant differences between the two groups in terms of their age, gender, presence of hepatitis C virus (HCV) infection, or clinical and symptomatic characteristics at baseline.

**Effectiveness results**
Clinical signs after 2 months of therapy improved in 18 (95%) of the 19 clobetasol-treated patients and in 13 (65%) of the 20 ciclosporin-treated patients. The difference was statistically significant, (p=0.04). Nine (47%) clobetasol-treated patients had complete remission of atrophic or erosive lesions versus 3 (15%) in the ciclosporin group, but the difference was not statistically significant.

Symptomatology improved in 18 (95%) clobetasol-treated patients and in 17 (85%) ciclosporin-treated patients, (p not significant). Complete remission of symptomatology occurred in 8 (42%) clobetasol-treated patients and in 4 (20%) ciclosporin-treated patients, (p not significant).

Eight patients (20%) were HCV positive. There was no correlation between the presence of the virus and the results of the therapy, nor did OLP treatment apparently influence liver outcome. None of the patients developed oropharyngeal candidosis.

Comparing the two treatment modalities, clobetasol gave significantly more side effects (dyspepsia, skin rashes and parotid swelling) than ciclosporin, (p=0.04).

After 2 months of follow-up, only 6 (33%) of the 18 clobetasol-treated patients whose clinical scores had improved were stable, compared with 10 (77%) of the 13 ciclosporin-treated patients who had shown improvement, (p=0.04).

**Clinical conclusions**
The study showed that topical ciclosporin provided comparable clinical efficacy, fewer adverse effects, and longer lasting remission of oral disease than topical clobetasol propionate. During follow-up, it was observed that patients treated with clobetasol were less stable than those treated with ciclosporin.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was used in the economic evaluation. The cost and effects were left disaggregated,
and the study was therefore classified as a cost-consequences analysis.

**Direct costs**
The direct total costs of the two treatments comprised the cost of the drugs and the cost of preparing them with the adhesive medium. All the dressings were prepared by the same pharmacy. The cost of antimycotics was not included in this evaluation as both patient groups used the same amount of them. The estimations of the quantities and costs were derived from actual data. Discounting was not carried out since the costs were incurred during less than 2 years. The quantities and the costs were analysed separately. The price year was not reported, nor was the source of the quantity and cost data.

**Statistical analysis of costs**
Only point estimates were reported. No tests of significance or confidence intervals were reported.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
Euros (EUR).

**Sensitivity analysis**
No sensitivity analysis was reported.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
No total costs of the interventions were reported.

The daily cost of ciclosporin treatment was EUR 1.82 compared with EUR 0.35 for clobetasol therapy.

The costs of adverse effects were not dealt with in the analysis.

**Synthesis of costs and benefits**
Not relevant.

**Authors' conclusions**
The study suggested that clobetasol propionate in 4% hydroxyethyl cellulose gel would currently appear to be more cost-effective than topical 1.5% ciclosporin in the same medium for the treatment of oral lichen planus (OLP). The main drawback of using ciclosporin routinely was its high cost. Even at very low concentrations, the daily cost of ciclosporin was more than five times higher than that of clobetasol.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparators used. Clobetasol appeared to be the most-effective topical steroid in the literature, while ciclosporin was a standard practice in the treatment of OLP. You should judge whether these drugs are relevant in your setting, or whether other comparators from other treatment or drug classes or dosages could have been
relevant as well.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised, controlled double-blind study, which is an appropriate design for the study question. The study had several main strengths. For example, power calculations were used to determine an appropriate sample size, the outcome assessment was blinded, and appropriate statistical analyses were undertaken to test for statistically significant differences between the two study groups. In addition, the study sample appears to have been representative of the study population, and the patient groups were shown to be comparable at analysis. These characteristics of the study suggest that the internal validity is likely to be high. There were no other sources of the effectiveness data.

Validity of estimate of measure of benefit
The authors did not derive a measure of health benefit. The reader is thus referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The perspective adopted in the economic analysis was not explicitly stated. However, it was not societal as no indirect costs were used in the analysis. Although not stated, some relevant costs could have been omitted from the analysis since the only costs considered were those of medications. This might have affected the authors' conclusions. The costs and the quantities were reported separately, which would enable the analysis to be easily extrapolated to other settings. However, the authors stated that they might possibly have underestimated the cost of ciclosporin. The sources of the cost data were not fully reported. The cost estimates were treated deterministically, and no sensitivity analysis was carried out to assess the robustness of the estimates used. All these factors could affect the robustness of the cost results. Discounting was not necessary since all the costs were incurred during less than 2 years. The price year was not reported, which will not help any future reflation exercises.

Other issues
Although the conclusions reflected the scope of the analysis, the authors compared their results with other relevant studies and found them to be different. The authors did not directly address the generalisability of the results to other settings. The authors recognised that they might possibly have underestimated the cost of ciclosporin, because the single lowest dose of ciclosporin solution that was available in Italy (5,000 mg) was probably too expensive for oral use in an adhesive medium. Also, they recognised that previous data had shown better results for clobetasol, perhaps because the drug was used for longer (6 months). Finally, considering that compliance in the ciclosporin arm was better because of the lower incidence of mild adverse effects, the importance adverse events have on patient compliance cannot be underestimated, especially since many patients in the study were elderly.

Implications of the study
Clobetasol propionate in 4% hydroxyethyl cellulose gel should probably be considered the treatment of choice for patients with atrophic or erosive OLP, whereas topical ciclosporin could represent a valuable second-line therapy. In addition, even though the whole data suggest that the adhesive medium might increase the effectiveness and daily dosage of a given drug, a direct pharmacological study on clobetasol and ciclosporin in hydroxyethyl cellulose is still lacking.

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