

Clinical and economic consequences of ozenoxacin vs. other topical antibiotics for the treatment of impetigo: a real-life study in Spain

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ABSTRACT

Background: Impetigo is a common dermatological paediatric infection that can be treated with topical antibiotics: the common are mupirocin (MUP), fusidic acid (FA) and, most recently, ozenoxacin (OZ).

Aim: This study assesses the clinical and economic consequences of the use of OZ vs. MUP and vs. FA for the treatment of impetigo in routine clinical practice in Spain.

Methods: This is a retrospective observational study using real-life data from electronic medical records of patients with impetigo who started treatment with OZ, MUP or FA (maximum follow-up: 3 months; n = 10,974). We compared treatment duration, comorbidities, use of systemic medication, complications, utilization of resources and associated costs across treatments (p<0.05). Cost-effectiveness of OZ was assessed from a social perspective. Complication rates and treatment duration were the effectiveness measures.

Results: Mean age was 12.6 (standard deviation [SD]: 16.6) years; 48.6% were male; treatment: 9.3% (OZ), 56.4% (MUP), 34.5% (FA). The percentage of patients ending treatment after 2 weeks was 87.6% (OZ) vs. 83.2% (MUP) vs. 82.4% (FA); p<0.001; complication rates were 1.8% (OZ), 3.3% (MUP) and 3.2% (FA), p<0.001; mean costs were €158 (OZ), €265 (MUP) and €287 (FA), p<0.001.

Conclusions: OZ is a cost-effective and dominant alternative for the treatment of impetigo.

Keywords: Cost-effectiveness, Impetigo, Ozenoxacin

Introduction

Impetigo is a common infection of the superficial layers of the epidermis that is mainly caused by *Staphylococcus aureus*, and less commonly caused by *Streptococcus pyogenes*. Impetigo causes lesions on the face, arms or legs of the patient, which are contagious and spread easily (1). Although it can affect patients of any age, it is more common in children aged 2 to 5 years, and accounts for approximately 10% of skin symptoms in the paediatric population (1). Impetigo can

have mild complications (pigmentation changes, cellulitis and recurrent infections, among other) and serious complications (glomerulonephritis and meningitis), although the latter are rare.

Diagnosis is generally based on symptoms and clinical manifestations alone, and treatment includes topical or oral antibiotics and symptomatic care. Antibiotics can reduce the duration and spread of the infection in specific situations (1). Among the topical antibiotics indicated for the treatment of impetigo are mupirocin (MUP), fusidic acid (FA) and ozenoxacin (OZ) (1).

When selecting treatment for impetigo patients, two main aspects should be considered. First, antimicrobial resistance, which has become a worldwide concern (2). Second, total cost of treatment, not only drug acquisition or early resources consumption, should be considered, as the presence of complications of impetigo can lead to a greater use of healthcare resources and associated healthcare costs (1). Hence, previous research has underlined the importance of assessing the clinical efficacy, duration of symptoms, prevention of recurrence and overall healthcare costs associated with different treatment options (2).

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OZ, a nonfluorinated quinolone, has been shown to have potent bacteriostatic and bactericidal activity against the most frequent Gram-positive pathogens associated with skin and soft tissue infections (3). Its efficacy and safety for the treatment of impetigo have been demonstrated in various clinical trials (3-5). However, the cost associated with the use of OZ and other topical antibiotics in the management of impetigo patients in routine clinical practice is uncertain. The objective of this study is to contribute to the available evidence of OZ's clinical and economic consequences, in comparison to other topical antibiotic treatments, in the management of impetigo in real medical practice in Spain.

Methods

We carried out a descriptive analysis of three study groups: (a) patients starting treatment with OZ, (b) patients starting treatment with MUP, and (c) patients starting treatment with FA, and we assessed the cost-effectiveness of OZ in comparison to topical MUP and FA for the treatment of impetigo, in routine clinical practice in Spain. The perspective of the study was that of society, with costs including healthcare costs and productivity losses for the adult population. Effectiveness parameters were clinical complication rates and length of treatment (as a proxy for patients' duration of symptoms).

We conducted a retrospective observational study using data from the BIG-PAC® (6) administrative database, which is representative of the Spanish population and includes primary data from anonymized and computerized medical records from public primary care centres and hospitals across seven autonomous communities in Spain ($n = 1.8$ million adult and paediatric patients). We selected patients who sought care and started treatment for impetigo with topical OZ, or MUP, or FA (index date), between 01 January 2018 and 30 June 2020. Additional inclusion criteria were: all ages, active patients in the database, patients whose regular follow-up could be ensured. We excluded patients that were transferred to centres not included in the database; permanently institutionalized patients; and patients with severe or terminal mental illness and/or on dialysis. Patient follow-up was defined as length of treatment, and maximum follow-up time was 3 months from index date. Healthcare resource utilization, temporary sick leaves and clinical complications were recorded during the follow-up period. Diagnosis and choice of treatment reflect the criteria and opinion of the physician in charge of the patient (routine clinical practice).

Clinical and demographic variables included in the analysis were: age, gender, comorbidities (asthma, atopic dermatitis, contact dermatitis, allergies, acne, wounds/burns, skin infections and immunodeficiencies), type of impetigo and previous episodes, length of treatment (index date to date of last visit to primary care, paediatrics, dermatology or hospital emergencies) and clinical complications (infection/abscess/cellulitis, lymphangitis/osteomyelitis, septicaemia/glomerulonephritis, ulcers, urticaria and dermatopaniculosis). Healthcare resource utilization included visits by type

of specialist (general practitioner, paediatrician, dermatologist), hospitalization and length of stay, hospital emergency visits, diagnostic tests and medication (including OZ, or MUP, or FA, and oral antibiotics, oral antihistamines and oral antifungals). The first line of treatment was defined as the medication administered from index date until the following 5 days, in accordance with the Summaries of Product Characteristics of the compared treatments. All subsequent medications (topical and systemic) were considered second-line treatment.

Unit costs imputed to resource utilization were obtained from the centres' analytical accounting (official Spanish National Health System tariffs): primary medical visit (€23.2), emergency visit (€117.5), medical speciality visit (€92.5), hospitalization (€568.0 per day) and laboratory tests (€32.3). Unit costs for medication were obtained from the pharmacy records included in BIG-PAC®. Temporary leaves were imputed the official average daily salary per day in Spain (€138.53) (7). All costs correspond to the year 2020.

Results

Demographic characteristics, and clinical and economic variables of the three study groups are summarized in Table I. Overall, 10,974 patients were included for analysis (mean age 12.6 [standard deviation (SD)]: 16.6) years; 48.6% male). By study group, 9.3% started treatment with OZ, 56.4% with MUP and 34.5% with FA. Patients treated with OZ were slightly younger than those treated with MUP or FA (mean age: 9.5 years [OZ] vs. 12.5 [MUP] and 13.6 [FA]; $p < 0.001$). In the first line of treatment, there was a similar percentage of systemic antibiotics dispensed (OZ: 42.8% vs. MUP: 43.3% and FA: 42.5%; $p = 0.743$). In the second line, this percentage was lower with OZ 20.2% vs. MUP 31.7% and FA 29.8%; $p < 0.001$). In addition, OZ was associated with a shorter duration of treatment (percentage of patients ending treatment in the first 2 weeks: OZ: 87.6% vs. MUP: 83.2% and FA: 82.4%; $p < 0.001$) and with a lower rate of complications (OZ: 1.8% vs. MUP: 3.3% and FA: 3.2%; $p < 0.001$). The most frequent complication was infection/abscess/cellulitis (total: 1.5%).

Total cost ($n = 10,974$) amounted to €2.9 million, of which 94.6% corresponded to the use of healthcare resources. Subjects who started treatment with OZ showed less use of healthcare resources than patients who started treatment with MUP or FA, especially with regard to primary care visits (1.9 vs. 2.8 and 2.7, respectively; $p < 0.001$), hospitalizations and length of stay (Tab. I). Hospitalization costs (39.3% of total cost), medication (26.8%) and primary care visits (23.5%) were the most prominent cost components. As the population included for analysis was mainly paediatric, labour productivity losses had little impact on total costs (5.4%). The average total cost per patient during the analysed period was lower with OZ (€158 vs. MUP: €265 and AF: €287; $p < 0.001$), respectively. No incremental cost-effectiveness ratios (ICERs) were calculated since management with OZ was found to be both less costly and more effective in terms of length of treatment (patient's responsiveness) and rate of complications than MUP and FA.

TABLE I - Baseline characteristics, complications, use of resources and costs per patient

Study groups	Ozenoxacin	Mupirocin	Fusidic acid	Total	p value
N, %	1,023 (9.3%)	6,185 (56.4%)	3,768 (34.3%)	10,974 (100%)	
Baseline characteristics					
<i>Demographics</i>					
Mean age in years (SD)	9.5 (12.0)	12.5 (16.3)	13.6 (18.0)	12.6 (16.6)	<0.001
Age ranges (%):					
0-9 years	75.7%	68.9%	66.6%	68.7%	
10-17 years	16.4%	15.9%	16.0%	16.0%	
18+ years	7.9%	15.2%	17.4%	15.3%	<0.001
<2 years	4.1%	5.0%	4.9%	4.9%	0.857
Gender, male	47.6%	48.5%	48.9%	48.6%	0.775
<i>Impetigo related</i>					
Bullous impetigo (diagnosis)	22.1%	22.5%	23.5%	22.8%	0.395
Previous episodes (temporal recurrence)	15.4%	15.5%	14.0%	15.0%	0.112
<i>Comorbidities</i>					
Asthma	8.9%	8.9%	8.2%	8.6%	0.456
Atopic dermatitis	26.9%	26.8%	26.1%	26.6%	0.725
Contact dermatitis	35.8%	35.3%	37.0%	35.9%	0.201
Allergies	15.2%	14.9%	13.6%	14.5%	0.154
Acne	2.2%	2.8%	3.6%	3.0%	0.019
Wounds/burns	3.3%	3.7%	3.1%	3.5%	0.203
Skin infections	3.4%	3.0%	3.3%	3.2%	0.695
Immunodeficiencies	1.9%	1.3%	1.5%	1.4%	0.284
<i>Specialist starting medication</i>					
General practitioner (GP)	28.7%	39.1%	39.5%	38.3%	<0.001
Paediatrician	70.8%	58.7%	55.5%	58.7%	<0.001
Dermatologist	0.3%	0.4%	3.1%	1.3%	<0.001
Other specialists	0.2%	1.8%	1.9%	1.7%	0.001
<i>Initial regimen (topic treatment)</i>					
Every 6 hours (4 times a day)	0.7%	2.7%	3.8%	2.9%	
Every 8 hours (3 times a day)	11.4%	4.7%	5.1%	5.5%	
Every 12 hours (2 times a day)	87.0%	87.5%	86.5%	87.1%	
Every 24 hours (1 time a day)	0.9%	5.1%	4.5%	4.5%	<0.001
<i>First line of treatment (initial)</i>					
Oral antibiotics	42.8%	43.3%	42.5%	43.0%	0.743
Oral antihistamines	31.2%	29.8%	31.1%	30.4%	0.339
Oral antifungals	0.6%	1.3%	1.6%	1.4%	0.034
Clinical Outcomes					
<i>Length of treatment (topic/oral)</i>					
1-2 weeks	87.6%	83.2%	82.4%	83.3%	
3-4 weeks	10.5%	14.0%	13.9%	13.6%	
5+ weeks	2.0%	2.8%	3.7%	3.1%	<0.001

(Continued)



TABLE I - (Continued)

Study groups	Ozenoxacin	Mupirocin	Fusidic acid	Total	p value
<i>Second line of treatment (follow-up)</i>					
Oral antibiotics	20.2%	31.7%	29.8%	30.0%	<0.001
Oral antihistamines	6.8%	11.0%	11.3%	10.7%	0.001
Oral antifungals	0.1%	0.2%	0.2%	0.2%	0.587
Topic treatment	5.5%	8.6%	7.0%	7.8%	<0.001
<i>Complications (%)</i>					
Infection/abscess/cellulitis	1.2%	1.7%	1.3%	1.5%	0.295
Lymphangitis/osteomyelitis	0.0%	0.0%	0.0%	0.0%	0.679
Septicaemia/glomerulonephritis	0.0%	0.0%	0.0%	0.0%	0.679
Ulcers	0.0%	0.1%	0.1%	0.1%	0.512
Urticaria	0.4%	0.8%	0.7%	0.7%	0.380
Dermatopaniculosis	0.2%	0.7%	1.0%	0.7%	0.011
Total complications	1.8%	3.3%	3.2%	3.1%	<0.001
Resource consumption					
Primary care visits (GP/paediatrician)					
Percentage of use (%)	100%	100%	100%	100%	0.999
Mean number of visits (SD)	1.9 (1.1)	2.8 (1.8)	2.7 (1.8)	2.7 (1.8)	<0.001
Visits to dermatology consultant					
Percentage of use (%)	1.1%	1.9%	3.8%	2.5%	0.006
Mean number of visits (SD)	0.1 (0.1)	0.2 (0.3)	0.2 (0.2)	0.2 (0.2)	0.002
Hospital emergency visits					
Percentage of use (%)	3.3%	3.7%	3.5%	3.6%	0.645
Mean number of visits (SD)	0.1 (0.2)	0.2 (0.5)	0.2 (0.7)	0.2 (0.6)	0.172
Laboratory tests/cytology					
Percentage of use (%)	2.6%	4.9%	4.9%	4.7%	<0.001
Mean number of tests (SD)	0.0 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.007
Hospitalizations					
Patients hospitalized (%)	1.4%	3.5%	3.7%	3.4%	0.001
Mean length of stay (in days) (SD)	0.1 (0.6)	0.2 (1.1)	0.2 (1.2)	0.2 (1.1)	0.001
Temporary leave					
Percentage of patients on TL (%)	0.4%	0.6%	0.7%	0.6%	0.758
Mean length of TL (SD)	0.1 (1.3)	0.1 (1.9)	0.1 (1.7)	0.1 (1.8)	0.735
Costs (average cost per patient)					
Primary care visits (GP/paediatrician)	44.0 (24.9)	64.1 (42.4)	62.6 (42.1)	61.7 (41.4)	<0.001
Visits to dermatology consultant	1.4 (13.8)	2.8 (25.5)	4.0 (20.8)	3.1 (23.1)	0.002
Hospital emergency visits	5.1 (29.0)	9.2 (62.4)	8.6 (77.4)	8.6 (65.8)	0.172
Laboratory tests/cytology	0.9 (5.9)	1.7 (7.7)	1.7 (7.8)	1.6 (7.6)	0.007
Hospitalizations	38.3 (341.9)	105.1 (625.3)	117.1 (667.9)	103.0 (620.3)	0.001
Medication (first line)	27.2 (9.2)	32.1 (7.0)	36.4 (6.2)	33.1 (7.5)	<0.001
Medication (second line)	32.0 (11.2)	36.5 (11.3)	40.5 (10.9)	37.5 (11.4)	<0.001
Healthcare cost	148.8 (351.5)	251.4 (648.7)	270.9 (698.0)	248.6 (645.7)	<0.001
Labour productivity losses	9.2 (182.4)	13.8 (263.6)	15.9 (234.2)	14.1 (247.2)	0.735
Total average cost per patient	158.0 (409.4)	265.2 (701.0)	286.9 (736.1)	262.7 (692.6)	<0.001

SD = standard deviation; TL = temporary leave.

Note: except for baseline characteristics, all measurements correspond to follow-up period; costs expressed in 2020 euros.



Discussion

Previous studies have proven higher cure and safety rates of OZ compared to other topical antibiotics in the treatment of impetigo (3-5). To our knowledge, this is the first study comparing both the clinical and the economic consequences of the management of impetigo patients with OZ vs. other topical antibiotics using real-life data. We found that, compared to MUP and to FA, OZ was associated with a shorter duration of treatment, lower complication rates, lower use of systemic antibiotics in the second line of treatment and lower use of healthcare resources. Average costs per patient were also significantly lower with OZ than with MUP or FA. As the management of impetigo patients with OZ was less costly and had better results than MUP and FA, our results indicate that OZ was a dominant treatment option compared to MUP and FA in real-life practice in Spain.

Our analysis is not without limitations. First, we do not consider clinical and economic consequences of no cure, of impetigo recurrence and of resistance to treatment. The measurement of such consequences would require a significantly longer follow-up period and was out of the scope of our objective. Second, in the assessment of the cost-effectiveness of OZ, we use length of treatment as one of two effectiveness parameters, with the underlying assumption that end of treatment implies a favourable response to treatment. End of treatment due to lack of efficacy, lack of adherence or appearance of adverse events is therefore not considered. However, the fact that previous literature has proven higher efficacy and lower complication rates of OZ compared to other topical antibiotics (3-5) suggests that our assumption is not unreasonable. Third, we did not carry out an age-adjusted comparison of clinical consequences and costs because this study aimed to shed light on real-life routine clinical practice for treating impetigo in Spain, including demographic differences in the population groups that are treated with each topical antibiotic. Finally, given that the vast proportion of patients with impetigo are children, schooling losses are likely to be an important component of the social costs of impetigo. Unfortunately, our database does not include appropriate data to approximate the cost of lost school time of patients, therefore precluding its inclusion and comparison across cohorts.

Conclusion

Despite the limitations in this study, our findings suggest that, in real clinical practice in Spain, the management of impetigo patients with OZ was associated with fewer use of healthcare resources, shorter length of treatment and lower complication rates than MUP and FA. Therefore, the use of OZ for the treatment of impetigo should be considered clinically and economically preferable.

Disclosures

Conflict of interest: ASM, RV and IPR are employees of Atrys Health, a contract research organization that received funds from Ferrer to conduct this study. All authors declare no conflicts of interest. Financial support: Ferrer, Spain, has provided financial support to cover the cost of this project, but has not influenced the manuscript content.

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