

Original article

Costs associated with persistent allergic rhinitis are reduced by levocetirizine

Background: Allergic rhinitis was recently classified by the ARIA guidelines as persistent or intermittent. Levocetirizine was shown to improve symptoms and health-related quality of life of patients with persistent allergic rhinitis in the XPERTTM study, a 6-month randomized double blind placebo-controlled trial.

Objective: To assess the total costs of persistent allergic rhinitis, and the effect of long-term treatment with levocetirizine on these costs from several perspectives (societal, social security system, and employers).

Methods: Direct medical cost parameters (medications, physician visits and hospitalizations) and time lost parameters (workdays and Usual Daily Activities (UDA) lost) related to persistent allergic rhinitis and its comorbidities (asthma, sinusitis, otitis and upper respiratory infection) were measured. A cost analysis was performed using 2002 French costing data.

Results: From a societal perspective, the total cost of persistent allergic rhinitis without long-term treatment was estimated at €355.06/patient/month. From a social security perspective, levocetirizine treatment yielded an additional cost of €2.78/patient/month, compared to no-treatment. However, levocetirizine reduced the total cost of persistent allergic rhinitis and its comorbidities by €152.93/patient/month from a societal perspective and by €64.70/patient/month from an employer perspective. Most gains resulted from a decrease in the lost workdays and UDA in the levocetirizine group.

Conclusion: The cost of persistent allergic rhinitis is substantial. Treatment with levocetirizine reduces the cost of persistent allergic rhinitis and its comorbidities to the society by €152.93/patient/month while improving symptoms and health-related quality of life.

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A new classification of allergic rhinitis (AR) into persistent or intermittent disease was proposed in 2001 by the Allergic Rhinitis and its Impact on Asthma (ARIA) committee sponsored by the World Health Organization (1). A recent epidemiological study conducted in France showed a clear difference between the prior classification and the ARIA revision in that only 55.4% of the perennial allergic rhinitis patients would now be categorized as persistent allergic rhinitis and 56.3% of the seasonal allergic rhinitis patients as intermittent allergic rhinitis (2). Another study, using the new classification, estimated the prevalence of allergic rhinitis in the general population in Western Europe at 22.7% among which 29% had persistent allergic rhinitis (3).

From a societal point of view, the cost of AR is significant because of the large number of patients suffering from the disease (4). However, very few studies have investigated the costs of AR in Europe. Much of what is known about the costs of AR is based on data from

the US (4). One study estimated the direct medical cost of AR in France at €510 million in 1997 (5). These costs are higher than those found for epilepsy (€340 million in 1998) (6, 7) or colorectal cancer (€470 million in 1999) (8) in France. Among the direct costs for AR, medications and physician visits are the primary cost drivers (9). Medications account for 24–68% and physician visits represent 32–73% of the total direct medical costs (10–12).

There also are costs associated with the time lost because of reduction in activities. These are important parameters for many pathologies such as arthritis, back pain, asthma, chronic headache or depression (13, 14). These time lost costs are those associated with productivity lost at work or the value associated with a loss of time for usual daily activities (UDA). While absenteeism because of AR appears to be low (12), many allergic sufferers may experience a loss of productivity (presenteeism) due to their disease as symptoms are often experienced while at work or at school (15, 16). Presenteeism

must therefore be included in the evaluation of time loss associated with AR (4). Patients with AR may also experience impairment outside work, referred to as time lost over daily activities (10, 15).

Allergic rhinitis shares common pathophysiologic components with asthma, otitis media, chronic sinusitis, upper respiratory infections and nasal polyps (17, 18). These diseases are therefore often associated and can be viewed as one overall disease. When these comorbidities are viewed as part of the continuum of AR disease, the overall cost of allergic rhinitis is considerable (19–21).

Nineteen percent to 45% of the AR patients do not receive a diagnosis (3, 22) and are therefore unlikely to be treated. For those treated, antihistamines often constitute the first-line treatment. In a previous publication, data from the Xyzal® in Persistent Rhinitis Trial (XPERT™) showed that levocetirizine improved symptoms and health-related quality of life of persistent AR patients when compared with placebo and also reduced the costs among working patients (23). The objectives of the current cost analysis is to assess the total cost (direct cost and costs related to workdays and UDA lost) of persistent AR and its comorbidities in the overall population (both working and nonworking), and to assess the monetary effect of a 6-month levocetirizine treatment on these costs.

Methodology

XPERT™, a levocetirizine placebo-controlled trial, was the first long-term (6 months) trial conducted in persistent AR (23). The trial was conducted in five countries (Belgium, France, Italy, Germany and Spain). The placebo group was used as a proxy for the no-treatment alternative.

Data collection

Both direct cost and time lost measures were collected alongside XPERT™. These parameters were associated with both persistent AR and its comorbidities. The targeted comorbidities were asthma, sinusitis, otitis and upper respiratory infections (18). Patients were followed over the entire 6-month period even in case of premature withdrawal from study medication.

Direct medical cost parameters

Direct medical costs are health care expenditures. In XPERT™, additional medications and unscheduled physician visits for persistent AR and its comorbidities were measured. Prior to unblinding, the XPERT™ chairman, an ENT physician, assigned the medical resources used to either persistent AR or comorbidity, based on a review of the coded indication or the

prescribing reason given. Medications for persistent AR (excluding levocetirizine) were further designated as per-protocol rescue medications (i.e. ocular/nasal cromoglycates and prednisolone) or as additional medications.

Time lost parameters

The time lost parameters were defined as the productivity lost at work and time lost over UDA because of persistent AR or its comorbidities. The workdays lost covered absenteeism as well as reduction of productivity while at work (presenteeism). The UDA covered leisure activities (e.g. sport, socializing, reading a book, etc.) as well as other usual activities such as housework, unpaid work in charities, etc. The time lost over UDA was composed of the inability to perform UDA as well as restriction in performing UDA. These data were collected weekly via a self-administered electronic diary. In the workdays lost section of the questionnaire, patients were asked to report the number of days with complete inability to work as well as any reduction in performance because of AR, asthma or other problems (infection/complication) affecting nose, eyes, ears and/or throat. Reduced performance was measured using both the number of days with reduced productivity and the level of productivity on those days on an 11-point scale (going from not able to perform work to able to perform work). The same approach was used to collect UDA lost.

Cost analysis

The cost analysis of all resources was performed from a French societal perspective using 2002 monetary values. France was selected as it was the country which most contributed to study recruitment (40.7% of patients).

Medications were assigned a daily cost. The daily costs were obtained from the VIDAL dictionary 2002. The 50 medications associated with the longest duration of use accounted for 90% of the total number of days under medications. VIDAL daily costs were only attributed to these 50 medications. Mean daily cost was assigned to the remaining medications. When the reported medication was not sold in France, a French equivalent was used based on the active molecule(s). Finally, a total medication cost was assigned to each patient as the sum of each medication daily cost multiplied by its duration of use. For the levocetirizine group, the cost of the 6-month study treatment was added using the initial market price in France (2003) i.e. €13.20 for 30 tabs (based on a 28-tab package).

Each unscheduled visit was assigned a cost corresponding to the 2002 tariff reported on the 'assurance maladie en ligne' website (<http://www.ameli.fr/>; accessed in May 2003), i.e. €17.50 for a GP visit and €22.90 for a specialist visit. Reimbursements from the social security system were retrieved from the same data sources.

A human capital approach was used to value workdays lost (24, 25). Each workday lost was assigned a mean

gross daily salary (i.e. including tax and other deductibles). The UDA lost was valued at its opportunity cost corresponding to the mean net daily salary (i.e. net of tax and other deductibles) (13, 25). These values were derived from the mean gross and net salaries in private and semi-public enterprises in 2002 provided by the 'Institut National de la Statistique et des Etudes Economiques' (<http://www.insee.fr/>; accessed in October 2004). Assuming 21.74 working days per month for the determination of the daily gross salary, each workday lost was valued at €106.76 while each UDA day lost was valued at €81.83 based on 30.44 days per month.

Perspective used

The perspective is the point of view used to determine the costs [i.e. employers are concerned about employees' productivity, while the society will also bear the costs of medications and time lost (workday and UDA lost)]. Three perspectives were investigated: the societal perspective i.e. all costs for all patients; a social security perspective i.e. reimbursement of direct medical costs for all patients; and an employer perspective i.e. costs of workdays lost by the working patients. The absenteeism was not taken into account in the social security perspective based on the assumption that it corresponded to short-term absenteeism (<4 days). This absenteeism would therefore not be paid by the French social security.

Sensitivity analyses

Three sensitivity analyses were performed based on the societal perspective. The first analysis was on the monetary value of workdays lost. The friction cost theory states that only part of the gross wage should be attributed to workdays lost due to compensation mechanisms (26). A threshold analysis on the costs difference between the two groups for the value of workdays lost ranging from €0 to €150/day was performed. The second sensitivity analysis addressed the uncertainty around the monetary value of an UDA day by assigning 25, 50 or 75% of the net daily salary to each UDA day lost. The results were thereafter compared to evaluate the impact of this valuation on the results. The third sensitivity analysis was to restrict the cost analysis to the French patients in order to assess possible differences between countries.

Statistical analysis

The direct cost and time lost parameters are presented in physical unit per patient and assigned a monetary value thereafter. Medical resources are presented over the 6-month evaluation period as mean number of visits for the physician visits and as mean duration of use (in days) for medications. The workdays (absenteeism, presenteeism and total work productivity lost) and UDA lost

(inability to perform UDA, restriction over UDA and total UDA lost) are presented as days lost/patient/month over the 6-month evaluation period. The presenteeism was computed by multiplying the reported number of days with reduced productivity by the reported level of productivity lost on those days. The same method was used to compute the restriction over UDA. The total workdays lost is the sum of absenteeism and presenteeism while the total UDA lost is the sum of inability to perform UDA and restriction over UDA. Costs were reported as euro value in 2002 per patient standardized to a 30-day month.

The frequency of unscheduled visits were analyzed and compared between treatment groups using a Poisson regression model with treatment as factor. All other parameters including costs were analyzed using a non-parametric bootstrap-t method. This technique is recommended when making inferences about arithmetic means for moderately sized samples of highly skewed data such as costs (27, 28). All analyses were performed on the intention to treat (ITT) population except the work productivity lost analysis which was restricted to employed ITT population. All analyses were performed with SAS version 8.1 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 551 subjects were randomized and included in the ITT population (273 in the no-treatment group and 278 in the levocetirizine group). The location and working status of the ITT population are presented in Table 1.

The medical resources used are presented in Table 2. Differences between the two groups were statistically significant (P -value < 0.05) for nasal cromoglycates (−40% relative to no-treatment), ocular cromoglycates (−55%), additional medications (−59%) for persistent AR (mainly antihistamines and glucocorticoids) and additional medications for comorbidities (−51%) (mainly beta-2 agonists, antihistamines and glucocorticoids). No

Table 1. Patient characteristics

	No-treatment group	Levocetirizine group	Total
Number of subjects (ITT population)	273	278	551
Location: <i>n</i> (% of group)			
Belgium	32 (11.7%)	33 (11.9%)	65 (11.8%)
France	114 (41.8%)	110 (39.6%)	224 (40.7%)
Germany	64 (23.4%)	68 (24.5%)	132 (24.0%)
Italy	42 (15.4%)	45 (16.2%)	87 (15.8%)
Spain	21 (7.7%)	22 (7.9%)	43 (7.8%)
Working status: <i>n</i> (% of group)			
Working	196 (72%)	186 (67%)	382 (69%)
Nonworking	77 (28%)	92 (33%)	169 (31%)

Table 2. Medical resources used over the 6-month evaluation period for persistent AR and for its comorbidities in the no-treatment and levocetirizine group (ITT population)

	Mean value per patient over 6 months [95% CI]	
	No-treatment (n = 273)	Levocetirizine (n = 278)
<i>Persistent allergic rhinitis</i>		
Additional medications (mean days per patient)†		
Per protocol rescue medications		
Nasal cromoglycates	23.23 [18.8–28.8]	14.04 [11.2–18.05]**
Ocular cromoglycates	14.38 [10.7–19.8]	6.51 [4.4–10.6]**
Prednisolone	0.79 [0.54–1.17]	0.67 [0.41–1.15]
Additional medications	23.38 [16.0–34.1]	9.52 [5.8–15.0]**
Physician visits (mean n per patient)‡	0.22 [0.17–0.28]	0.18 [0.13–0.23]
<i>Comorbidities</i>		
Additional medications (mean days per patient)†	22.70 [15.5–33.4]	11.12 [7.4–17.3]*
Physician visits (mean n per patient)‡	0.17 [0.12–0.22]	0.17 [0.12–0.22]

CI, confidence interval.

* $P < 0.05$, ** $P < 0.01$.

†CI computed with a nonparametric bootstrap-t method.

‡CI computed with a Poisson regression model.

Table 3. Mean workdays lost per month per working patient over the evaluation period

	Mean days/patient/month [95% CI]	
	No-treatment (n = 196)	Levocetirizine (n = 186)
Absenteeism	0.45 [0.30–0.77]	0.18 [0.13–0.26]**
Presenteeism	1.05 [0.83–1.33]	0.70 [0.54–0.92]*
Total workdays lost	1.49 [1.18–1.96]	0.88 [0.70–1.13]**

CI, confidence interval computed with a bootstrap t procedure.

* $P < 0.05$, ** $P < 0.01$.

difference was observed between levocetirizine and no-treatment for unscheduled visits.

The time lost parameters over the evaluation period are presented in Table 3 for workdays lost and in Table 4 for UDA lost. Both workdays lost and UDA lost, over the evaluation period, were lower in the levocetirizine group than in the no-treatment group as assessed by the statistically significant difference between the treatment groups. The improvement with levocetirizine (i.e. reduction in the number of lost days) relative to the no-treatment group was larger for total loss over UDA (+1.39 day per month per patient) than for total workdays lost (+0.61 day per month per working patient).

The results of the conversion of these data into monetary value using a French societal perspective are presented in Table 5. The total costs obtained from all perspectives investigated are presented in Fig. 1.

From the societal perspective, the total mean monthly cost per patient in the levocetirizine group was €202.12

Table 4. Mean usual daily activities (UDA) days lost per month per patient over the evaluation period

	Mean days/patient/month [95% CI]	
	No-treatment (n = 273)	Levocetirizine (n = 278)
Inability to perform UDA	1.45 [1.16–1.84]	0.64 [0.50–0.84]***
Restriction over UDA	1.45 [1.22–1.73]	0.88 [0.72–1.10]***
Total loss over UDA	2.90 [2.41–3.51]	1.51 [1.24–1.88]***

CI, confidence interval computed with a bootstrap t procedure.

*** $P < 0.001$.

Table 5. Monetary valuation of medical resources used and time lost per 30 days month per patient from a French societal perspective

	Mean €/patient/month [95% CI]		
	No-treatment (n = 273)	Levocetirizine (n = 278)	Bootstrap t P -value
<i>Direct medical costs</i>			
Persistent allergic rhinitis			
Levocetirizine	0	13.20	
Medications	4.61 [3.86–5.44]	2.35 [1.92–2.92]	0.002
Physician visits	0.71 [0.44–1.12]	0.84 [0.49–1.70]	0.66
Comorbidities			
Medications	2.51 [1.58–4.50]	1.32 [0.82–2.40]	0.08
Physician visits	0.54 [0.36–0.84]	0.47 [0.32–0.69]	0.58
<i>Value of lost time</i>			
Absenteeism	33.90 [23.73–55.53]	12.83 [9.29–18.47]	0.001
Presenteeism	79.01 [63.95–99.05]	49.10 [38.30–64.01]	0.007
Inability to perform UDA	117.16 [95.99–147.38]	51.25 [40.67–66.54]	0.001
Restriction over UDA	116.63 [100.56–137.03]	70.75 [59.24–86.42]	<0.001
Total costs	355.06 [300.68–428.41]	202.12 [171.84–243.21]	<0.001

CI, confidence interval computed with a bootstrap t procedure.

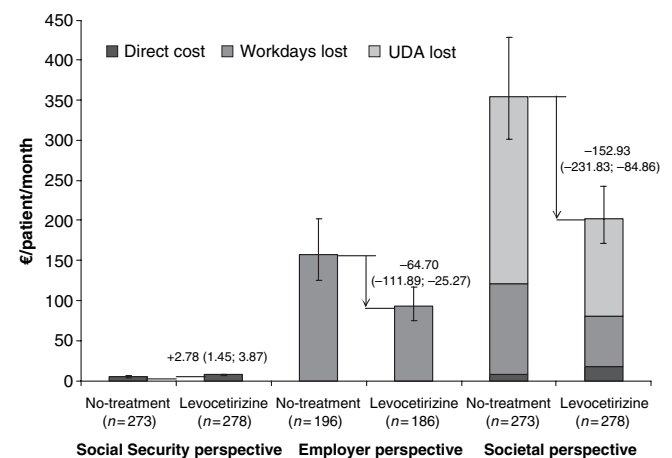


Figure 1. Cost per treatment group for the social security perspective, the employer perspective and the societal perspective.

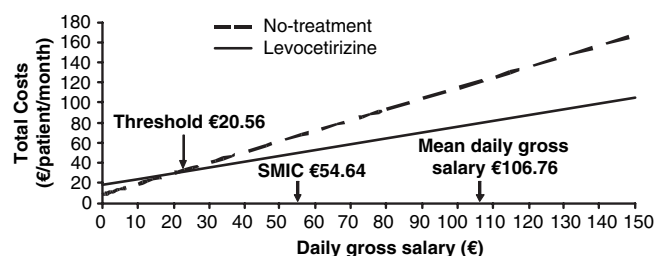


Figure 2. Threshold analysis on the value assigned to a work-day lost, ranging from €0 to €150. The SMIC is the official minimum daily wage in France (2002 value).

(95% CI: 171.84–243.21) compared with €355.06 (95% CI: 300.68–428.41) in the no-treatment group. This corresponded to a €152.93 gain/patient/month (95% CI: 84.86; 231.83; P -value < 0.001) or a 43% cost reduction over the costs of persistent AR with no treatment. When only absenteeism was taken into account as time lost cost, the gain was €11.24 (95% CI: 0.36; 32.76; P -value = 0.09). From a social security perspective, restricted to direct medical costs reimbursed, the levocetirizine group costs an additional €2.78/patient/month (95% CI: 1.45; 3.87, P -value < 0.001) compared with the no-treatment group. From an employer perspective, which excludes medication costs and physician visits, the gain was €64.70 per working patient per month (95% CI: 25.27; 111.89; P -value < 0.001).

The results of the first sensitivity analysis are presented in Fig. 2. The threshold value (i.e. €0 saving with levocetirizine) was observed for workdays lost valued at €20.56 (i.e. 19% of the mean gross salary used to value workdays lost, €106.46). In the second sensitivity analysis, total costs remained in favor of levocetirizine in all cases with a €77.61 (95% CI: 37.85; 128.45; P -value < 0.001) gain/patient/month when valuing a UDA days lost at the lowest bound of the UDA day monetary valuation (25% of the net daily salary). The third sensitivity analysis (restricted to the 224 French patients) showed a gain for the levocetirizine group of €200.94 per patient per month (95% CI: 103.44; 329.72; P -value < 0.003) over the no-treatment group.

Discussion

The total costs measured in the no-treatment group, from a societal perspective (€355.06/patient/month) can be considered as the overall cost for a patient with persistent AR without long-term treatment. The direct medical costs constituted 2% of the total cost while workdays lost and UDA lost represented 32% (mainly presenteeism: 22%) and 66% respectively (equally due to inability to perform UDA and restriction over UDA) of the total costs.

All cost parameters, direct and time lost, showed an improvement in the levocetirizine treatment group

compared with the no-treatment alternative. When converted into monetary value it appears that the benefit with levocetirizine reaches €152.93/patient/month from a societal perspective and €64.70 from an employer perspective. The costs in the levocetirizine group were, however, slightly higher, from a social security perspective (+2.78) than in the no-treatment group because of levocetirizine drug cost. For the same reason, from a societal perspective, direct medical costs linked to persistent AR are also larger in the levocetirizine group (16.39/patient/month) than in the no-treatment group (5.32/patient/month). These direct costs are in accordance with the upper bound values of monthly costs per patient found in the literature for AR i.e. in the US \$4.32 in 1990 (10); \$13.56 in 1996 (29) or in France €4.93 in 1998 (5). In the XPERTTM evaluations, higher costs may be related to the inclusion of comorbidity costs. Absenteeism ranged from 0.18 days/patient/month in the levocetirizine group to 0.45 days in the no-treatment group. These values are larger than AR absenteeism previously reported in the literature [0.005 (11) to 0.37 (15) days/patient/month]. This may be due to the fact that, among AR patients, persistent AR patients have long-term and probably more severe disease.

The patients reported days lost for persistent AR as well as for specific comorbidities, which could lead to a higher number of workdays lost. In this study, UDA covered leisure activities as well as other activities such as unpaid work. It is important to take both workdays and UDA lost into account from an equity point of view. By doing so, an overall estimate of the time lost can be obtained for working and nonworking patients, both of whom contribute to society output. Additional comparisons are difficult given the lack of studies in the literature with the type of patients and parameters included in XPERTTM (4).

There are limitations to this evaluation. Measured costs may underestimate both the burden encountered by patients in real practice settings and the difference in costs between patients treated with levocetirizine vs no-treatment. Six physician visits were prescheduled, implying a careful follow-up of patients and probably lowering the need for use of additional medical resources. Moreover, rescue medications were monitored, limiting the type and number of medications taken by patients. All these factors, in addition to the placebo effect, may increase benefits in the no-treatment group and reduce the differences between groups.

In addition some types of costs such as nonmedical direct costs (e.g. house adaptation, transportation to visits) were not monitored in this study. The overall costs of persistent AR and its comorbidities in real practice may therefore be higher.

There are some uncertainties about the true monetary value that can be assigned to workdays and UDA days lost. However, even with a low estimate for workdays or UDA days lost, the levocetirizine group yielded benefit over no-treatment.

Another possible limitation is the use of French costs for all patients. However, when the analysis was restricted to the French patients, the difference obtained between the two groups (€200.94) was within the 95% confidence interval of the difference obtained when pooling patients from all countries. This further confirms the transferability of these results to other countries.

In addition to the generating cost savings as observed, levocetirizine treatment was previously shown to improve rhinitis symptoms and patients' health related quality of life as measured by either rhinitis specific (RQLQ) or generic health-related quality of life questionnaire (SF-36) (23). Given the burden associated with persistent AR, treatment with levocetirizine could therefore substantially improve the life of those who suffer from that disease.

Conclusion

The costs of nontreated persistent AR and its comorbidities are substantial for the society. These costs can be reduced through a long-term treatment with levocetirizine.

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