Quality of life scale and impact of a topical treatment on symptoms of gastro-esophageal reflux without severe esophagitis

Interest of the MOS SF-36 questionnaire

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SUMMARY

Objective — Restoring a normal quality of life (QOL) should be the goal of treatments of gastro-esophageal reflux (GER) without severe esophagitis. In this analysis, carried out within the frame of a clinical study comparing a topical anti-inflammatory gel to a placebo, we assessed the relevance of the MOS SF-36 questionnaire in patients suffering from GER without severe esophagitis, and compared the scores of the studied patients to those of a representative sample of the French general population.

Patients and methods — The patients had to suffer from GER symptoms for at least 2 months, with no or mild (grade 1) esophagitis endoscopically. They were randomized to be given a 4 week treatment either with a topical gel containing gaiazulene and dimeticone or a placebo gel. Patients were asked to complete a symptom diary during the study, which allowed the calculation of mean symptom scores. The MOS SF-36 questionnaire was administered at baseline (d0) and after 4 weeks of treatment (d28).

Results — Two hundred and thirty three patients were enrolled in the study. At baseline, QOL scores were impaired in both groups. After 4 weeks of treatment, the treated patients displayed a better improvement in all MOS SF-36 domains compared with the placebo group. The QOL profile in the treated group reached the level of the French reference population, while it remained impaired in the placebo group.

Conclusion — This analysis evidenced the relevancy of the MOS SF-36 questionnaire to assess the impact of GER without severe esophagitis on QOL. Moreover, it demonstrated the capacity of the studied topical treatment to restore a normal QOL to the patients.

In France, over a third of the population suffers from reflux symptoms. In the majority of cases, these troubles are occasional, developing by brief eruptions of similar severity levels, during a few days to a few weeks, interrupted by long periods of remission.

Hygiene-dietetic measures intend to eliminate reinforcing factors, whereas medicine-based treatments aim to either lessen reflux symptoms, reduce the aggressiveness of the refluxate, or limit the amount and duration of reflux [2].

GER literature data bring to the fore the poor concordance between the severity of mucosal damage at endoscopy and symptoms intensity [3]. In case of reflux entailing minor endo-

RÉSUMÉ

Échelle de Qualité de Vie et impact d’un traitement topique sur les symptômes de RGO sans œsophagite sévère : intérêt du questionnaire MOS SF-36

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Objectif — Le but du traitement du reflux gastro-aéosophagien (RGO) sans œsophagite sévère devrait être de restaurer une qualité de vie (QDV) normale. Dans cette analyse, menée dans le cadre d’un essai clinique comparant un gel topique anti-inflammatoire à un placebo, nous avons évalué la pertinence du questionnaire MOS SF-36 chez des malades souffrant de RGO sans œsophagite sévère, et comparé leurs scores à ceux d’un échantillon représentatif de la population française.

Patients et méthodes — Les malades souffraient de RGO depuis au moins 2 mois, sans lésion endoscopique ou avec au plus une œsophagite de grade 1. Après randomisation, ils étaient traités 4 semaines soit par un gel topique en sachet contenant du gaïazulène et du diméticone, soit par un gel placebo. Ils devaient reporter leur évaluation de leurs symptômes quotidiennement sur un carnet, ce qui a permis le calcul d’un score symptomatique moyen. Le questionnaire MOS SF-36 a été complété à l’inclusion (J0) et après 4 semaines de traitement (J28).

Résultats — Deux cent trente-trois malades ont été inclus. A l’inclusion, les scores de QDV étaient altérés dans les 2 groupes. Après 4 semaines de traitement : l’amélioration du groupe traité était plus importante que celle du groupe placebo, dans toutes les dimensions du MOS SF-36. Le profil de QDV du groupe traité et celui de la population française de référence étaient comparables, alors qu’il restait altéré dans le groupe placebo.

Conclusion — Cette analyse a mis en évidence la pertinence du questionnaire MOS SF-36 dans l’évaluation de l’impact du RGO sans œsophagite sévère sur la QDV. Elle a par ailleurs montré que le traitement topique étudié pouvait restaurer une QDV normale.

Introduction

Gastro-esophageal reflux (GER) without severe esophagitis is a benign condition that can however be sometimes incapacitating due to the recurrence of disturbing symptoms that alter patients’ quality of life (QOL) [1].

In France, over a third of the population suffers from reflux symptoms. In the majority of cases, these troubles are occasional, developing by brief eruptions of similar severity levels, during a few days to a few weeks, interrupted by long periods of remission.

Hygiene-dietetic measures intend to eliminate reinforcing factors, whereas medicine-based treatments aim to either lessen reflux symptoms, reduce the aggressiveness of the refluxate, or limit the amount and duration of reflux [2].

GER literature data bring to the fore the poor concordance between the severity of mucosal damage at endoscopy and symptoms intensity [3]. In case of reflux entailing minor endo-
scoposcopic lesions or not, the impact of a treatment on symptomatology and its consequences on patients’ well-being become all the more important. Given the fact that clinical studies show that GER symptoms alter QOL, the efficiency of a GER treatment could be defined by its capacity to restore a normal QOL [4], particularly when no objective parameter can be evaluated. The experts at the consensus conference on “diagnosis and treatment of gastroesophageal reflux in adults” [5] underlined that, in all cases, the therapeutic objective should be the relief of symptoms and a return to a normal QOL. In cases of severe and complicated esophagitis, and only in those, they admit as therapeutic objective the healing of lesions and the prevention of recurrences.

Consistently with these recommendations, they advocate the use of QOL questionnaires and the evaluation of reliable and standardized symptoms through clinical trials.

In this article, we present the analysis of quality of life measurements collected within the framework of the controlled clinical trial of a topical gel associating a local anti-inflammatory principle (gaïazulene) and a mucosa-protector compound (dimeticone) administered for 4 weeks to subjects suffering from symptomatic GER without severe esophagitis [6].

This analysis has three objectives: 1/ to verify the relevance of this instrument in evaluating the QOL of subjects suffering from GER and to estimate the accuracy of the measurements obtained, 2/ to study the evolution of QOL scores for subjects suffering from GER (in term of effect size), 3/ to compare control and treated subjects QOL scores obtained at d0 and d28 to scores obtained from a representative sample of the French general population paired in terms of age and gender.

The stake of these analyses is to validate the QOL parameter as a main result indicator in GER without severe esophagitis.

Populations and methods

The trial was carried out in liberal practice (56 physicians-investigators out of which 90% were general practitioners and 10% were gastroenterologists).

Study population

Patients had to display GER symptoms (at least one amongst: heartburn, gastric burning sensation, regurgitation) for at least 2 months, with a minimum frequency of 3 times per week and a severity score superior or equal to 2. These symptoms had to be persistent despite hygienodietetic measures applied for at least 7 days. An initial endoscopy dating from less than 2 months had to show a normal esophagus or a grade 1 esophagitis in the Savary-Miller classification. The patients were randomized to receive either a topical gel in sachet containing gaïazulene (4 mg) and dimeticone (3 g) or a placebo gel (3 to 6 sachets/day).

Reference population

The reference group was constituted by individuals belonging to a population representative of the general French population based on its main variables known to influence responses to QOL questionnaires (age, gender, marital status, occupation, education level, geographic situation, etc.). Four thousand QOL questionnaires were sent out by the SOFRES Medical Survey Agency to subjects aged 15 years and above; 500 questionnaires were sent out to an oversample of subjects aged 65 years and above (the objective of this oversampling was to obtain a better accuracy in cells concerning elderly persons). Eighty three percent of subjects belonging to the main sample (N = 3308) and 70% of subjects belonging to the oversample (N = 348) filled out and sent back the questionnaire. A weighting coefficient has been calculated in order to make the population of questioned subjects representative of the overall French population.

Pairing method

Each subject recruited within the trial framework was paired to 30 subjects from the reference population in the same gender and age bracket (the age variable was broken down by age section of 5 years: 15-19, 20-24, …80-84). In order to obtain robust and accurate results, the random sampling was performed 30 consecutive times, with a re-introduction after each draw. The QOL scores were calculated by working out the average of the 30 draws, in order to increase the accuracy of the estimation (the standard deviation being the average of the 30 standard deviations).

Symptom scores

The symptoms (heartburn, gastric burning sensation and/or regurgitation) were evaluated daily by the patient according to their severity (graded from 0 to 3) and their duration (graded from 0 to 3) (table I).

The score of each symptom was the product of severity and duration grades (i.e.: 0 to 9). The daily symptomatic score was defined as the sum of scores obtained for each symptom (i.e.: from 0 to 27). This evaluation allowed the calculation of an average global symptomatic score defined as the mean of daily symptomatic scores for the basal period from d-7 to d0 and for each half therapeutic period from d1 to d14 and from d15 to d28.

Quality of life questionnaires

The Medical Outcome Study Short Form 36 (French version 1.3) [7-10] includes 36 questions grouped into 8 dimensions: physical functioning (PF), role emotional (RE), bodily pain (BP), general health (GH), mental health (MH), role physical (RP), vitality (VT) and social functioning (SF). A score is calculated for each of these dimensions. The total set of scores constitutes the MOS SF-36 profile. There is no global score; however, two second-order summary scores, the physical composite score (PCS) and the mental composite score (MCS), can be calculated from the scores of each under-scale. The French version of MOS SF-36 offers good psychometric properties [11].

Calculation of the number of subjects and statistical analysis

The main evaluation criterion was the percentage of patients showing a decreasing of at least 50 per cent of the average global symptomatic score as compared to the pre-inclusion period basal score.

The secondary evaluation criteria were the symptomatic evaluation realized by the physician and his global appreciation of the efficiency at each visit, the calculation of the areas under the curve of symptomatic scores taking into account the actual number of self-evaluation days (in relation to the maximum weekly score), the clinical tolerance and the evolution of the MOS SF-36 quality of life profile between d0 and d28.

Table I – Definitions of severity and duration grades for each symptom (heartburn, gastric burning sensation, regurgitation).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptom</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>Slight symptom of spontaneous remission, not interfering with daily activity or sleep</td>
<td>&lt; 1.5 min</td>
</tr>
<tr>
<td>2</td>
<td>Moderate symptom, regressing spontaneously but slowly and interfering with daily activity or sleep</td>
<td>Between 1.5 and 30 min</td>
</tr>
<tr>
<td>3</td>
<td>Severe symptom, not spontaneously regressing and interfering much with daily activity or sleep</td>
<td>&gt; 30 min</td>
</tr>
</tbody>
</table>
With a percentage of patients improved by the placebo estimated to 50% and in order to evidence a gain of therapeutic success of 25% with a first order risk equal to 5% and a power of 95%, 90 patients were needed in each group. Estimating that approximately 20% of the patients would potentially be lost track of, 110 patients had to be included and randomized in each treatment group.

The analysis was carried out on an intent to treat basis. All the tests were performed in bilateral formulation. The type 1 error was set to 5% for the overall study.

The non-ordered qualitative variables were described by the numbers, percentages and reliability range of the percentage. The 2 groups were compared with the Chi2-test or a Fischer's exact test when the numbers were too low.

The ordered qualitative variables were described by the numbers and percentages of all the different categories. The groups were compared with a Wilcoxon-test.

The continuous quantitative variables were described by their mean, standard deviation, minimum and maximum, median and quartiles in the case in which distributions were showing a strong dissymetry. The comparisons of the 2 groups were realized with a Student-test or by a non-parametric approach (Wilcoxon-test).

The main objective of the MOS SF-36 psychometric analysis was to verify the conformity of the results with the hypothesis underlying the score constructions in Likert type scales [12] constituting the MOS SF-36 (the score is calculated by simple summation of the items). There were 5 hypothesis: each question must be correlated by at least 0.4 with the dimension to which it contributes ; the questions must be more correlated with their dimension than with the other dimensions ; the items measuring a same concept must approximately have the same means and the same variances ; all the questions of a same underscale must have approximately the same correlation with this underscale [without the question] ; the accuracy of scores, estimated for instance by Cronbach's coefficient alpha, must be superior to 0.7 for group comparisons.

In order to evaluate the evolution of the answers to MOS SF-36 obtained from subjects belonging to control and treated group, we have calculated, for each underscale of the MOS SF-36 and for each group of subjects, the standard difference (effect size) corresponding to the difference between the mean of the group at d28 and at d0 divided by the standard deviation at d0. These standard differences, expressed in standard deviation units, make comparisons between groups easier, quantitatively and visually [13] and, in addition, allow to estimate the subjective significance (as opposed to statistic) of a measured difference: it is generally admitted that a difference of 0.4 to 0.5 standard deviation is subjectively perceived by the subjects.

Programs used

EXCELE 2000 (Microsoft); SAS v. 8.1 [SAS institute], Multitrait Analysis Program Revised (MAP-R).

Results

Patients characteristics

Two hundred and thirty three patients were included in the trial. 117 in the treated group and 116 in the placebo group. The differences of exposure to the treatment, measured by the global observance of the 2 groups are not statistically significant. Nineteen patients out of 117 in the treated group and 24 out of 116 in the placebo group had a grade 1 esophagitis (NS). For all the other patients, initial endoscopy was normal. Twenty-one patients from the treated group and 28 from the placebo group dropped out of the study (NS). The motives of premature discontinue of the treatment are comparable in the two groups: intercurrent event (N = 6), therapeutic failure (N = 9), deviation from the protocol (N = 24), premature success (N = 3), or other reason (N = 7). Patients characteristics are described in table II.

Clinical evaluation

All these clinical results have been described elsewhere [6]. Briefly, the tolerance was good: 6 patients from the treated group and 10 from the placebo group displayed at least one adverse event with moderate or low intensity. Only one case of severe flatulence was reported in the placebo group.

On an intent to treat basis, the total of patients who obtained an improvement of 50% and more of their symptomatic score was superior in the treated group at d14 with an estimated success gain of 13% in comparison to placebo (respectively 54.14% and 41.1%; IC 95%: 3.9-2.9 %). Furthermore, the evolution of areas under the curve for symptomatic scores turned out to be in favor of the treated group, during the d1-d14 period (P < 0.01) as well as during the d15-d28 period (P < 0.02).

As to the global evaluation of the treatment efficiency, carried out by the investigator at the end of the study, the superiority of the treatment among the "clear improvement" group was statistically significant (52% versus 37%; P = 0.05).

Qualities of quality of life measurements

The response rate to the QOL questionnaire was high (90%). The floor and ceiling effects (collected percentages of extreme values, high or low) are relatively important for the RP and RE dimensions. The ceiling effects are moderate for the PF and SF dimensions.

The results of multitrait analysis show that the hypothesis regarding the construction of scores are satisfied. Generally speaking, the MOS SF-36 questions are more correlated to the dimension (scale or underscale ) to which they belong than with the other dimensions. They are never better correlated with another dimension. The inter-scale correlation is relatively homogenous. The highest correlation is observed between the “mental health” and the “vitality” scale, which is consistent with the conceptual structure of MOS SF-36. The accuracy of the measurements obtained with MOS SF-36 is good. The Cronbach’s coefficient alpha is, for instance, always superior to 0.7 (0.71 to 0.9), which allows comparisons between groups.

Analysis of quality of life results

At the time of inclusion, there were no differences of average quality of life profiles. The treated group shows better scores than the

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Table II – Patients’ characteristics at inclusion time (d0).

<table>
<thead>
<tr>
<th></th>
<th>Verum</th>
<th>Placebo</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>45/72</td>
<td>39/77</td>
<td>84/149</td>
<td>NS</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>50.6</td>
<td>49.0</td>
<td>49.8</td>
<td>NS</td>
</tr>
<tr>
<td>Average weight (kg)</td>
<td>67.6</td>
<td>67.6</td>
<td>67.6</td>
<td>NS</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>166.0</td>
<td>165.5</td>
<td>165.8</td>
<td>NS</td>
</tr>
<tr>
<td>Associated diseases (_1%)</td>
<td>53.8</td>
<td>51.7</td>
<td>52.8</td>
<td>NS</td>
</tr>
<tr>
<td>Socio-professional situation (%)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>61.5</td>
<td>64.7</td>
<td>63.1</td>
<td></td>
</tr>
<tr>
<td>retired</td>
<td>26.5</td>
<td>19.8</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>at home</td>
<td>7.7</td>
<td>9.5</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Initial endoscopy (%)</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Normal esophagus</td>
<td>54</td>
<td>52</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Grade 1 esophagitis</td>
<td>19</td>
<td>24</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Symptomatic score (mean )</td>
<td>7.6</td>
<td>7.8</td>
<td>7.7</td>
<td>NS</td>
</tr>
</tbody>
</table>
topical treatment and QOL in GERD

placebo group in 3 MOS SF-36 dimensions: vitality (P < 0.036), social functioning (P < 0.048) and mental health (P < 0.021).

The analysis of standard differences shows that the improvements observed between d0 and d28 are systematically more important in the treated group than in the placebo group (figure 1).

A global improvement was observed in both patient groups during the therapeutic period. The importance of score improvements is different between the two groups. It is of course important to find out whether such variations are perceived by patients. There is no consensus regarding the existence of a threshold from which an effect size is subjectively perceived. It is however admitted that the higher the effect size is, the more important the difference is felt to be.

A comparison of standard differences between treated and placebo groups (figure 1) shows evidence of differences superior to 0.4 for 5 out of 8 MOS SF-36 dimensions (as well as for both summary scores, physical and mental) in the treated group versus only one dimension (BP) in the placebo group.

If we consider a more conservative score of 0.5 standard deviation, 2 MOS SF-36 dimensions (BP-bodily pain and SF-social functioning) are improved in a perceivable way in the treated group whereas only the BP dimension is improved in the placebo group.

Comparison with the general population

Differences of answers to MOS SF-36 between the two studied groups and those paired to them, representative of the general French population, were calculated at d0 and d28.

The observation of MOS SF-36 answers for subjects belonging to both treated and placebo groups shows that the subjects QOL tends to get closer to the general population’s between d0 and d28.

The analysis of differences between MOS SF-36 scores from treated and placebo subjects and those from the sample of the French general population shows the following evolution: at d0, MOS SF-36 scores for treated and placebo groups are significantly different from those from the comparison group. After 4 weeks of treatment, responses to MOS SF-36 from patients belonging to the treated group are no longer significantly different from those belonging to the general population except for the MH and GH dimensions (table III), whereas responses from patients belonging to the placebo group remain significantly different from those from the comparison group in every MOS SF-36 dimension (table IV). In other words, it is possible to affirm that the treatment’s effect “normalized” the quality of life of subjects suffering from GOR.

Discussion

Beyond the symptomatic improvement, the treatments’ objective is to restore the subjects’ QOL. The final purpose of treatment

<table>
<thead>
<tr>
<th>Table III. – Evolution of the MOS SF-36 scores in comparison to the general population (Treated group).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Group</td>
</tr>
<tr>
<td>d0</td>
</tr>
<tr>
<td>PF</td>
</tr>
<tr>
<td>RP</td>
</tr>
<tr>
<td>BP</td>
</tr>
<tr>
<td>GH</td>
</tr>
<tr>
<td>VT</td>
</tr>
<tr>
<td>RE</td>
</tr>
<tr>
<td>SF</td>
</tr>
<tr>
<td>MH</td>
</tr>
<tr>
<td>PCS</td>
</tr>
<tr>
<td>MCS</td>
</tr>
</tbody>
</table>

* NS
of GER without severe esophagitis is primarily to relieve symptoms and, in the rare most severe forms, to heal lesions and prevent complications.

The results of the psychometric analysis of MOS SF-36 answers from patients in the present study are overall similar to those previously described in the literature [4] and validate the use of MOS SF-36 in this population suffering from GER without severe esophagitis.

The analysis of the standardized difference (effect size) evolution allows to interpret more accurately the meaning of statistically significant differences which are observed on subjects after 4 weeks of treatment or placebo. The question is to know whether statistically significant QOL improvements are actually perceived by the affected subjects.

The analysis of results allows us to say that the effect of treatments is subjectively perceived (effect size superior to 0.4) by subjects in dimensions RP, BP, VT, RE, SF and MH measured by MOS SF-36 as well as in the two second-order dimensions, mental (MCS) and physical (PCS). On the other hand, the placebo effect only corresponds to a perceived improvement for the BP dimension in MOS SF-36. Whatever threshold should be considered as relevant, the subjects from the treated group enjoy a greater subjective improvement of their QOL than the improvement generated by the placebo effect. It is therefore possible to conclude that the treatment improves QOL by its own effect. In that sense, it satisfies to the first objective of any treatment of GER without severe esophagitis as expressed by the above mentioned consensus conference.

Another objective of GER treatment is to restore a normal QOL. In order to estimate whether this objective is achieved, we have compared the scores from subjects included in the trial with those from a reference group in the general population, comparable in terms of age and gender. The result of the analysis is remarkably clear:

I/ QOL in treated and placebo groups is significantly different from the general population’s before treatment, which reflects the impact of GER. II/ placebo subjects’ quality of life remains significantly inferior to the general population’s for all MOS SF-36 scales, III/ on the other hand, after 4 weeks of treatment, the treated group subjects’ QOL had become indiscernible from the general population’s (it no longer showed statistically significant differences for 5 out of 7 MOS SF-36 dimensions for which a difference had been observed at inclusion time). In other words, the subjects’ QOL had returned to being ‘normal’ in terms of health condition impact on bodily pain (BP), Vitality (VT), social functioning and activities (SF, RP and RE). The results having been obtained within a double blind, placebo-controlled trial, this evolution can be imputable to the treatment. It is therefore possible to affirm that, in patients suffering from GER without severe esophagitis, the studied treatment administered during 4 weeks allowed to restore a normal QOL or at least a health condition perceived as normal [14].

It should be noted that these results are in line with those analysed by Revicki et al. [1] in the case of the impact of ranitidine in the US population. Actually, the comparison of our study sample with a comparable group of the French general population in term of the main variable known to be predictors of QOL score -which Revicki et al. did not do- increases the validity of our results of our study. It should be noted that such a comparison with the general population and the demonstration of the ‘normalization’ of the QOL of the subjects in the treatment group could not have been obtained with any of the disease specific instruments that have been developed (eg the Reflux-qual [15]) given the absence of any general population reference data for such instruments. Indeed, one may question the utility of these disease specific instruments when the impact of GER without severe esophagitis can be readily demonstrated with a generic measure of quality of life such as the MOS SF-36.

In conclusion, this study illustrates the relevance of QOL measurements to evaluate the impact of GER treatment in complement with traditional indicators (morbidity and symptoms). It also demonstrates the interest of using a rigorous analysis methodology to interpret the results of QOL studies when adequately carried out. It finally evidences the effective impact of the studied treatment and its capacity to respond to the objectives expressed by the consensus conference regarding the diagnosis and the treatment of gastro-esophageal reflux in the adult population.
namely to ‘normalize’ the QOL of the subjects suffering from GER without severe esophagitis. This result is all the more remarkable and valid since it has been demonstrated by the analysis of the responses of the subjects to a standard generic instrument which has not been designed with the purpose of maximizing the effect of GER on QOL.

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