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Supplementary prevention and management of asthma with quercetin phytosome: a pilot registry

Running header: Quercetin phytosome in asthma management

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ABSTRACT

In association with standard management, natural PS (pharmaceutical standard) supplements may play an important role in managing and preventing mild-to-moderate symptoms of asthma, a significant health issue that impacts patients and the healthcare system. Quercetin is a natural flavonoid with important biological properties (anti-inflammatory, antihistamine and anti-oxidative actions). In this pilot registry, we evaluated the effects of quercetin formulated with the Phytosome® delivery system (Quercefit™, QFit) + standard management (SM) in otherwise healthy subjects with mild–moderate asthmatic attacks and rhinitis. Subjects used either QFit 1 or 2 caps/day in association with SM or SM only (control group). After 30 days of management, we evaluated the presence of the main signs/symptoms of asthma according to the GINA classification system also considering the need of rescue medication, nasal drops, the use of inhalers, the rhinitis score and oxidative stress.

QFit + SM showed superior results compared with SM alone in controlling, preventing and reducing daily and night symptoms, in maintaining higher peak expiratory flow (PEF) and in decreasing PEF variability. The supplementary use of QFit improved additional measures of asthma management, decreasing the use of inhalers, nasal drops, rescue medications and improving the rhinitis score. QFit produced a significantly more evident reduction in oxidative stress compared with SM; Qfit showed a very good safety profile.

This preliminary supplement, concept registry shows a potential protective and preventive effect of quercetin on attacks frequency and in controlling the most common signs/symptoms of asthma in the milder cases of the disease.

RIASSUNTO

Gli integratori naturali prodotti secondo standard farmaceutici possono, in associazione ai trattamenti standard, svolgere un ruolo importante nella gestione e nella prevenzione

dell'asma in forma lieve-moderata, una patologia che ha un profondo impatto sia sui pazienti che sul sistema sanitario. La quercetina è un flavonoide naturale con importanti proprietà biologiche tra le quali un'azione antinfiammatoria, antistaminica e antiossidante. In questo studio pilota abbiamo valutato gli effetti della quercetina formulata con il sistema di rilascio Phytosome® (Quercefit ™, QFit) in combinazione con un protocollo di gestione standard (SM) in soggetti altrimenti sani con attacchi asmatici e rinite in forma lieve-moderata. I soggetti hanno ricevuto QFit 1 o 2 capsule al giorno in combinazione con SM o solo SM (gruppo di controllo). Dopo 30 giorni di trattamento abbiamo valutato la presenza dei principali segni/sintomi dell'asma secondo il sistema di classificazione GINA, considerando inoltre l'uso di farmaci di salvataggio, di gocce nasali, di inalatori, la gravità della rinite e il livello di stress ossidativo.

La combinazione di QFit + SM ha mostrato risultati superiori rispetto a SM da solo nel controllare, prevenire e ridurre i sintomi giornalieri e notturni dell'asma, nel mantenere un picco di flusso espiratorio (PEF) più elevato e nel diminuire la variabilità del PEF. L'uso di QFit ha migliorato altri parametri di gestione dell'asma, diminuendo l'uso degli inalatori, delle gocce nasali e dei farmaci di salvataggio e migliorando la rinite. Infine, QFit ha portato a una riduzione significativamente più evidente dello stress ossidativo rispetto al solo SM e ha mostrato un ottimo profilo di sicurezza.

Questo studio preliminare di registro mostra un potenziale effetto protettivo e preventivo della quercetina nella riduzione della frequenza degli attacchi e nel controllo dei segni/sintomi più comuni dell'asma nei casi più lievi della malattia.

KEY WORDS mild-to-moderate asthma, rhinitis, quercetin, oxidative stress, rescue medication

INTRODUCTION

The management of asthma and the prevention of attacks in subjects with mild-to-moderate symptoms is a significant problem that affects healthcare systems and is a distressing problem for many patients and general practitioners (GPs). The management and prevention of asthma is well defined. Chronic therapy may expose patients to significant side effects and may result in high healthcare costs.[1,2]

Symptoms – particularly when mild–moderate – tend to affect otherwise healthy subjects in the working age population, with loss of working days and increased number of medical consultations.[1,2] According to the GINA (Global Initiative for Asthma) Classification[2] asthma standard management (SM) consists,in most patients, of controlling triggering factors, in improving patients' education also managing of acute phases and is based on drug therapy. The main drug classes used in asthma treatment include bronchodilators (β2 agonists, anticholinergics), corticosteroids, leukotriene modifiers, mast cells stabilizers, methylxanthines and immunomodulators.[2–4]

Environmental aspects are essential in asthma management.[1,2]

High-quality, well-characterized PS supplements manufactured according to pharmaceutical standards may improve signs/symptoms and avoid the frequent use of more important (and side-effects prone) treatments, including corticosteroids, particularly in borderline, non-severe patients.[1,2]

Quercetin is a natural flavonoid widely found in vegetables, fruits and nuts, which has important biological activities, including antioxidant, antinflammatory, antimicrobial, antibacterial and antiviral properties.[5-7]

As seen in a recent pilot study, quercetin, formulated with the Phytosome® delivery system (Quercefit™, also called QFit), appears to block histamine release in healthy subjects undergoing the histamine challenge test.[8] This procedure consists of a micro-injection of histamine into the superficial forearm, which causes a local reaction with different prominence, elevation and redness areas in different individuals. The lesion also disappears at different time rates in different individuals. In subjects with asthma, the wheal tends to be more elevated, the erythematous area is larger and its persistence tends to be more prolonged. Corticosteroids (and antihistamines) attenuate the reaction and shorten the presence of the skin wheal.

The preventive administration of QFit to healthy volunteers for 3 days tends to decrease the elevation and area of the wheal, also enabling the disappearance of the lesion and the surrounding erythema in a significantly shorter time (Figure 1).[8] Similar results were obtained with the topical administration of Quercevita®, a similar formulation of quercetin Phytosome®, in healthy volunteers undergoing the histamine challenge showing the ability to reduce the response, possibly associated to basophils degranulation.[7,9] Recent experiences with QFit also indicate its beneficial effects in sport/fitness and in controlling oxidative stress.[10,11]

The aim of the present pilot study was to evaluate the preventive effects of QFit supplementation, in association with well-defined standard management (SM) in otherwise healthy subjects with mild–moderate asthmatic attacks and rhinitis. The registry also had the aim of evaluating whether the supplement may decrease the use of other medications including corticosteroids and broncodilators.

PATIENTS AND METHODS

This was a pilot, registry, supplement study.

Supplement studies are aimed to define the field of activity of supplements and possible preventive, preferably non-clinical applications.[12-16] These studies are designed and organized with the full attention and participation of the evaluated subjects. The best field of application for supplements are pre-disease, borderline applications or the supplementary management of some risk conditions. Supplements – unless specific claims are present – are not generally used for treatment of severe signs/symptoms or conditions of clinical relevance.

Supplement studies are open-label studies; no placebo is used. Patients are always informed about the supplement or any treatment and management measure they will receive, and the products under evaluation are not prescribed but recommended. In these types of studies, control groups – generally using a standard management - if present, are not necessarily parallel.

Patients. Subjects with both asthma and rhinitis were included into the registry and received QFit either 1 cap/day or 2 caps/day for 30 days in combination with SM. Subjects in the control group were maneged according to asthma SM therapy and received either corticosteroids or bronchodilators (β2 agonists, anticholinergic). No antihistamine drugs were used.

The GINA Classification of Asthma Severity[2,4,17] was used to select patients: all subjects included were in GINA class 1 (intermittent) and 2 (mild persistent); whereas more severe subjects (GINA classes 3 [moderate persistent] and 4 [severe persistent]) were excluded.

The study was conducted in spring, when, according to patients, symptoms become more common and frequent.

Measures evaluated. The main items considered from the GINA system and from the Merck Manual[1] were:

1. Presence of daily symptoms;
2. Presence of night symptoms;
3. Improvement in peak expiratory flow (PEF)/forced expiratory volume (FEV);
4. Improvement (decrease) in PEF variability.

The most disturbing symptoms as indicated in the GINA platform and reported in the Merck Manual[1] were considered.

Also, the following accessory items were considered in the evaluations:

5. The use of the inhaler, only when needed according to patient information leaflet (Ventolin® - GSK).
6. The rhinitis score, assessed on a visual analogue scale line with an arbitrary score from 0 to 4;
7. The use of nasal drops (Otrivin®; Novartis) – on demand only;
8. The possible use of rescue medications (e.g. corticosteroids, Bentelan® 1 cap 0.25 mg, Sigma-Tau).
9. The occurrence of side effects during the supplementation period was also considered.

Oxidative stress was separately considered as an accessory parameter (not within the GINA platform). Oxidative stress was measured as plasma-free radicals (PFRs) with a FRAS analyzer in peripheral blood (one single drop of blood); PFRs were measured in standardized Carr units. The method has been validated in several clinical and population studies.[18]

External study reviewers. All results and data were evaluated by an external reviewing panel, not in contact with the registry patients. Safety and tolerability were assessed by weekly contacts and laboratory measurements. Possible adverse experiences were evaluated throughout the registry in terms of intensity (mild, moderate or severe), considering duration, seriousness, outcome and relationship to the study supplement.

Statistical Analysis. Descriptive statistics was used to evaluate the clinical effect of the supplementation on the chosen parameters. On the basis of the statistical model it was estimated that at least two groups of more than 20 subjects were needed to assess any difference in target parameters after the period of supplementation. Non-parametric statistics was used to evaluate the differences between the groups. The differences in the management groups were analyzed using the ANOVA (with Bonferroni correction) and the Mann-Whitney U-test[19] and the X^2 test (intima-media thickness, IMT, Oxidative stress).[20]

RESULTS

Overall 30 subjects were managed with QFit + SM: a group of 20 subjects received QFit 2 caps/day (250 mg per capsule) for 30 days on top of SM while a second group of ten cases was managed with QFit 1 cap/day. In total, 28 subjects were included in the SM-only group. There were two drop outs (none of the patients deteriorated) in the QFit + SM group, with a total of 28 patients who completed the study out of 30 initially included, versus three drop outs and five deteriorated subjects registered in the SM-only group (eight completion out of 28 inclusions). The percentage of patients dropping out, not included in the intention to treat analysis, was 4.32-times greater for the SM-only group compared with the QFit + SM group (28.57% vs 6.6%; $p<0.023$) (Table 1).

The baseline characteristics of subjects included in the QFit + SM group are reported in Table 2.

All subjects supplemented with QFit + SM, showed a more significant decrease in daily symptoms, night symptoms, a better improvement in PEF/FEV_1 and an improvement (decrease) in PEF variability compared with subjects managed with SM only (Table 3). In particular, subjects using the higher dose of QFit supplementation had significantly better results ($p<0.05$) in both symptomatic groups 1 and 2 (Table 3).

Table 4 shows the results of accessory evaluations, including the use of the inhaler when needed, the rhinitis score, the use of nasal drops (on demand only), the use of rescue medications and, the occurrence of any side effects.

QFit supplementation + SM reported superior results compared to the SM only, with the higher dose of QFit being more effective for most of the items ($p<0.05$). Rescue medications were used in 3/20 subjects (15%) in the QFit + SM group versus 8/28 (28.56%) in the SM group ($p<0.05$).

No side effects were observed in both groups. The application of the SM was satisfactory in all subjects and the safety profile of QFit was considered very good, with optimal tolerability with both doses and no subjects who had to stop the supplementation.

Blood tests were normal at inclusion and at the end of the study, particularly hepatic parameters (bilirubin, SGOT, SGPT and phosphatase). Kidney parameters (creatinine and urinary proteins) and hematocrit were within normal values at baseline and at the end of the study.

Oxidative stress as PFR was above normal values in all subjects at inclusion; it Oimproved (decreasing) after 30 days of treatment with QFit + SM, and the effect was significantly more evident ($p<0.05$) with the higher dose compared with SM alone (Table 5).

DISCUSSION

QFit supplementation appears to offer a possible better management compared with SM alone in preventing the occurrence and worsening of asthmatic attacks.

QFit has shown a significant activity in improving performance, respiratory function and recovery after a significant sport effort in healthy individuals performing a triathlon at non-professional level.[21] Moreover, a recent non-interference, non-interaction registry study has indicated that QFit does not interfere with antiplatelet prevention, anticoagulants and anti-diabetic treatments.[22]

This new formulation has improved and more consistent oral absorption[23] thanks to the new specific Phytosome® formulation technology.[23] The optimization of the formula components and its absorption are a significant, clinically important aim in the use of this class of products of natural origin.[23]

The powerful anti-inflammatory activity of quercetin has been shown also in a recent study, which reported its effects in inhibiting the production of IL-1β-induced inflammatory cytokines and chemokines in ARPE-19 cells via the MAPK and NF-κB signaling pathways.[24] Another study has shown that quercetin reduces visceral hypersensitivity in patients with irritable bowel syndrome, in which histamine and inflammatory factors, also observed in asthma, may be present and play a significant role.[25]

Clinical parameters and evolution of asthma management are changing with the progressive improvement in environmental conditions in the working place and in most homes.[26] There is now an increasing attention towards a 'soft' management approach, not including heavy medications and corticosteroids or drugs known for altering patients' quality of life (i.e. anti-histamine drugs).

As shown in our pilot study, the use of QFit combined with asthma SM may help control the most disturbing symptoms of the disease, reducing the presence of daily and night symptoms, maintaining higher PEF/FEV_1 and reducing PEF variability. Notably, the combination of QFit with SM also improved additional measures of asthma management, decreasing the use of inhalers, nasal drops, rescue medications and rhinitis score.

Finally, QFit + SM seems to be more effective than SM alone in decreasing oxidative stress, as measured by the PRFs in peripheral blood. The presence of reactive oxygen species has been recognized, together with inflammation as a key biochemican hazard for the genesis and development of asthma symptoms.[27,28]

In this pilot registry, the best results were obtained with the administration of QFit 2 caps/day, with superior results compared to SM alone and better outcomes compared to the lower dose.

In conclusion, this preliminary concept-registry shows a potential protective effect of quercetin in decreasing attacks frequency and controlling most common signs/symptoms in the milder cases of asthma, in otherwise healthy individuals. Future studies should be conducted on a higher number of patients with more complex situations and variable conditions and followed for longer periods to further evaluate the potential supplementary role of quercetin in asthma management.

NOTES

A. There is no conflict of interest for the authors

B. These results, data and their interpretation cannot be used for meta-analysis without a specific consent from the authors.

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Tables

TABLE 1: Intention to treat analysis.

	Quercefit™ + SM, patients (n)	**SM, patients (n)**
Included	30 10 (1 cap/day) + 20 (2 caps/day)	28
Deteriorated	0	5
Drop-out	2	3
Total ITT analysis (n; % loss)	2/30 (6.6%)	8/28 (28.57%)
ITT: Intention to treat; SM: standard management.		

TABLE 2: Characteristics of subjects included in the study according to GINA classification

Group	Characteristics				Included patients		
	Symptoms - day	***Symptoms - night***	***PEF/FEV₁***	***PEF variability***	***N. (M/F)***	***Mean age (SD), years***	***Treatment***
Step 1: intermittent	<1 time a week (asymptomatic with normal PEF between attacks)	≤2 times/month	≥80%	<20%	12 (6 males/6 females)	34.6 (2.2)	Quercetin + SM (2 caps/day)
					10 (4 males/6 females)	35.1 (3.1)	Quercetin + SM (1 cap/day)
Step 2: mild persistent	>1 time/week but <1 time/day (attacks may affect activity)	>2 times/month	≥80%	20–30%	8 (4 males/4 females)	35.8 (8.3)	Quercetin +SM (2 caps/day)
Step 3: moderate persistent	Daily (attacks affect activity)	>1 time/week	60–80%	>30%	Excluded from the study		
Step 4: severe persistent	Continuous (limited physical activity)	Frequent	≤60%	>30%	Excluded from the study		

PEF: peak expiratory flow; FEV_1: forced expiratory volume in the first second; SM: standard management; SD: standard deviation;

TABLE 3: Evaluation of most severe symptoms in subjects managed with Quercetin + SM vs SM only

Treatment	Symptoms - day (times/week)		Symptoms - night (times/month)		PEF/FEV (%)		PEF variability (%)	
	Baseline	***30 days***	***Baseline***	***30 days***	***Baseline***	***30 days***	***Baseline***	***30 days***
Step 1: intermittent								
Quercetin + SM (2 caps/day)	0.72 (0.2)	0.35 (0.3)*	1.64 (0.4)	0.5 (0.3)*	72.4 (2.3)	83.6 (1.9)*	16.2 (2)	7.2 (0.5)*
SM only	0.71 (0.3)	0.5 (0.2)	1.6 (0.3)	1 (0.3)	71 (2.2)	80 (2)	16 (0.8)	11.5 (0.4)
Quercetin + SM (1 cap/day)	0.7 (0.1)	0.44 (0.2)*	1.68 (0.2)	0.67 (0.2)*	73 (2)	81.5 (1)*	16.2 (2)	11.3 (0.3)*
SM only	0.68 (0.2)	0.52 (0.2)	1.61 (0.2)	1.1 (0.2)	72 (2.1)	79.3 (1.2)	16 (0.8)	11.4 (0.2)
Step 2: mild persistent								
Quercetin + SM (2 caps/day)	1.4 (0.3)	0.7 (0.4)*	2.7 (1.6)	1.4 (0.3)*	71 (0.4)	76.2 (2)*	24.3 (1)	18.4 (2.2)*
SM only	1.42 (0.5)	1.1 (0.3)	2.63 (1)	2 (0.8)	72.2 (1)	13.2 (0.6)	24 (0.8)	20.3 (2)

*statistically significant ($p<0.05$)

TABLE 4: Accessory evaluations in subjects managed with Quercetin + SM vs SM only

Treatment	Use of inhaler in 30 days (% of reduction)	Rinitis score 0–4 (SD)		Use of nasal drops in 30 days (NUMBER OF APPLICATION)	Use of asthma rescue medications (n of patients)	Side effects
		Baseline	***30 days***			
Step 1: intermittent						
Quercetin + SM (2 caps/day)	-28	3.2 (0.4)	1.7 (0.3)	11	1	0
SM only	-18	3.1 (0.3)	2.7 (0.6)	42	3	–
Quercetin + SM (1 cap/day)	-24	3.3 (0.2)	1.8 (0.4)	18	2	0
SM only	-19	3.2 (0.3)	2.4 (0.4)	40	3	–
Step 2: mild persistent						
Quercetin + SM (2 caps/day)	-33	3.6 (0.4)	1.81 (0.3)	14	1	0
SM only	-18	3.5 (0.4)	2.6 (0.4)	34	3	–

TABLE 5: Variations in oxidative stress in subjects managed with Quercetin + SM vs SM only.

Treatment	**Oxidative stress; Carr units (SD)**	
	Baseline	***30 days***
SM only	388.4 (21)	378 (13)
Quercetin + SM (2 caps/day)	382 (13)	322 (14)*#
Quercetin + SM (1 acp/day)	377 (16)	341 (15)*

SD: standard deviation; SM: standard management.

best result