Lymphology 29 (1996) 29-35

# TREATMENT OF SECONDARY LYMPHEDEMA OF THE UPPER LIMB WITH CYCLO 3 FORT

R.V. Cluzan, F. Alliot, S. Ghabboun, M. Pascot

Unité de Lymphologie, Hôpital Cognacq-Jay, Paris, France

*ABSTRACT*

*Fifty seven patients with secondary lymphedema of the upper limb after previous treatment for breast cancer were treated for 3 months with an extract of Ruscus + Hesperidin Methyl Chalcone (CYCLO 3 FORT) or placebo according to a double-blind protocol in the context of a controlled clinical trial. All patients also underwent manual lymphatic drainage twice a week for at least one month. With CYCLO 3 FORT, the reduction in volume of arm edema, the main assessment criteria, was 12.9% after 3 months of treatment as compared with a placebo (p=0.009). Decreased edema tended to be more marked in the forearm compared with the upper arm where excess fat deposition seemed to dominate over excess fluid accumulation.*

*CYCLO 3 FORT was well tolerated with minimal adverse reaction.*

Demonstration that several drugs are able to modify the intrinsic pumping function of lymphatic vessels and to activate tissue macrophages and hence proteolysis of sequestered macromolecules has raised the possibility of effective drug treatment for peripheral lymphedema. One class of these compounds belongs to the benzopyrone group, although confusion sometimes surrounds use of the generic term "benzopyrones" because these agents may differ from one another or be poorly defined as, for example, in plant extracts. Regardless of the mechanism of action of each drug, however, demonstration of true efficacy requires a controlled application under the rigor of a clinical trial. Thus far, the clinical efficacy of drug treatment for lymphedema has consistently appeared to be less than that of "compression therapy" (e.g., manual lymphatic treatment, elastic support, wrapping-bandages) (1) but lack of a controlled clinical trial for each therapeutic modality (e.g., operative, drug, physiotherapy) continues to generate a wide difference of opinion as to the optimal treatment program for patients with peripheral lymphedema.

Accordingly, we carried out a controlled clinical trial in treatment of secondary lymphedema using a plant extract possessing venotonic and lymphotonic properties and marketed in France under the trade name of CYCLO 3 FORT. This medication contains two active ingredients, an hydroalcoholic extract of Ruscus Aculeatus and Hesperidin Methyl Chalcone.* The pharmacologic action of this drug as tested in experimental animals includes "venotonic enhancement" (i.e., greater venous motility) (2,3), reduction in experimental edema (4), and "improved" microcirculatory function (5). Hesperidin Methyl Chalcone has been classified as a bioflavonoid, compounds thought to decrease microvascular permeability and to increase microvascular resistance to blood flow.

*Each capsule of CYCLO 3 FORT contains 150 mg of Ruscus Aculeatus extract, 150 mg of Methyl Hesperidin Chalcone and 100 mg of ascorbic acid.

Ruscus Aculeatus extract contains mainly steroid saponins (ruscogenin and neoruscogenin) as the active biologic component (6). A dose-dependent vascular contraction has been demonstrated on isolated saphenous veins, a biologic action that can be suppressed by an α-adrenergic blocker (phentolamine) and partly inhibited by the vasoactive modulators prazosin and rauwolscin. Biologic activity of Ruscus extract derives from a combination of displacement of stored norepinephrine from presynaptic neuronal vesicles and by direct activation of postjunctional α1 and α2 adrenergic receptors of venous smooth muscle cells.

Other experimental results have also shown activity of Ruscus extract on the lymphatic system. Thus Ruscus extract induces a dose-dependent increase of lymphatic flow (7) an action that appears to be mediated by the adrenergic system (8) as previously shown on the venous system (6). McHale (8) also demonstrated a dose-dependent increase of spontaneous lymphatic contractions after administration of Ruscus extract. Moreover, in a preliminary open clinical trial, Jimenez-Cossio et al (9) demonstrated the positive action of Ruscus extract plus Hesperidin Methyl Chalcone in patients with lymphedema based on a lessening of symptoms, reduction of the volume of edema and improved tracer transport on lymphoscintigraphy.

## *PROTOCOL*

### *Study Design*

This single-center trial was conducted in the lymphology unit of Cognacq-Jay hospital in Paris. It was a randomized, double-blind controlled study (CYCLO 3 FORT versus placebo).

### *Patient Population*

Fifty seven adult women (>18 years of age) presenting with lymphedema of the upper limb after radiotherapy or surgery for breast cancer were studied. In order to participate in the trial, each patient had to accept the principle of the study and give a written, informed and free consent. The principal evaluation criterion consisted of the difference (in centimeters) of the circumference of the affected arm compared to the intact, contralateral arm. This circumference difference was calculated every 5 cm from the antecubital fossa (with the arm outstretched). Four measuring points were determined from the antecubital fossa to the distal part of the forearm and 3 other points from the antecubital fossa to the proximal part of the upper arm. Circumference differences were also calculated at the wrists and hands. A total of 10 measuring points were determined in each arm.

Patients were included in the study when the circumference differences of the affected (swollen) arm to healthy (nonedematous) arm were more than 2 but less than 8 cm on at least one measuring point. Lymphedema was classified into two categories: mild (circumference arm difference of more than 2 but less than 5 cm) and moderate (circumference arm difference of more than 5 but less than 8 cm). Each group was randomized to receive either CYCLO 3 FORT or placebo.

Patients with active or recurrent cancer, systemic or cutaneous infection, diabetes mellitus or heart, renal, or hepatic failure were excluded. Concomitant drugs likely to influence the course of edema, such as diuretics and benzopyrones, were prohibited or discontinued for at least one month before inclusion into the study. Morbidly obese patients (Body Mass Index greater than 32) were excluded. Patients previously treated by manual lymphatic drainage, however, were accepted provided that they had been treated for at least one month with two physiotherapy sessions per week.

## *EVALUATION CRITERIA*

### *Efficacy*

**TABLE 1**
**Edema Reduction of the Whole Upper Limb**
(calculated by the difference between the affected arm and the contralateral non-edematous arm)

| Patient Group | D30 (%) | D60 (%) | D90 (%) |
|---|---|---|---|
| **CYCLO 3 FORT** | | | |
| Mild lymphedema | -03.55 | -17.14 | -20.67 |
| Moderate lymphedema | -00.35 | -05.53 | -10.35 |
| Total | -01.16 | -08.50* | -12.90** |
| **PLACEBO** | | | |
| Mild lymphedema | -08.81 | +04.99 | +05.65 |
| Moderate lymphedema | +02.79 | +00.32 | +01.89 |
| Total | -00.48 | +01.20 | +02.55 |

*CYCLO 3 FORT>placebo p=0.03; **CYCLO 3 FORT>placebo p=0.009; D=day

**TABLE 2**
**Edema Reduction in the Upper Arm**

| Patient Group | D30 (%) | D60 (%) | D90 (%) |
|---|---|---|---|
| **CYCLO 3 FORT** | | | |
| Mild lymphedema | -10.91 | -17.16 | -23.34 |
| Moderate lymphedema | +03.36 | -03.02 | -07.66 |
| Total | -00.08 | -06.37* | -11.18** |
| **PLACEBO** | | | |
| Mild lymphedema | -09.81 | +09.16 | +08.75 |
| Moderate lymphedema | +02.40 | -00.45 | -00.83 |
| Total | +00.01 | +00.01 | +00.76 |

*CYCLO 3 FORT>placebo p=0.03; **CYCLO 3 FORT>placebo p=0.01; D=day

The main criterion adopted for evaluation of efficacy was the percentage of swelling reduction in terms of the volume of edema. Edema volume was determined by adding the volumes of the truncated cones calculated from the circumferences measured every 5 cm in the arm and forearm (10).

Secondary criteria for efficacy consisted of subjective improvement (recorded on a visual analogue scale, taking into account the mobility of the affected limb, feelings of heaviness and softness), as assessed by both

**TABLE 3**
**Edema Reduction in the Forearm**

| Patient Group | D30 (%) | D60 (%) | D90 (%) |
|---|---|---|---|
| **CYCLO 3 FORT** | | | |
| Mild lymphedema | +02.54 | -17.12 | -18.60 |
| Moderate lymphedema | -03.78 | -07.96 | -12.97 |
| Total | -02.13 | -10.50 | -14.47** |
| **PLACEBO** | | | |
| Mild lymphedema | -08.14 | +02.07 | +03.44 |
| Moderate lymphedema | +03.07 | +00.93 | +04.04 |
| Total | +00.70 | +01.16 | +03.93 |

**CYCLO 3 FORT>placebo p=0.02

the patient and investigator. These criteria were evaluated on day 0 (D0), day 30 (D30), day 60 (D60), and day 90 (D90).

*Side Effects (Safety)*

At each visit, each patient was questioned regarding any untoward side effects which were then catalogued.

*TREATMENT*

Each patient received 3 capsules of active drug (i.e., CYCLO 3 FORT) or placebo, 3 times a day. The two test substances were supplied in the form of capsules with an identical appearance. The patients were asked to return surplus capsules at each visit in order to assess compliance with treatment.

*RESULTS*

*Patient Population*

Demographic comparison between the groups did not reveal statistically significant differences with the exception of Body Mass Index, which was higher in the CYCLO 3 FORT group than in the placebo group, but which nevertheless remained within the limits defined by the protocol. All other parameters were statistically comparable between the "active" drug and placebo groups including oncological parameters (site of tumor, type of cancer treatment), clinical course of edema (progressive onset in 2/3 of patients), distribution and type of lymphedema (mild lymphedema: 12 in the CYCLO 3 FORT group and 12 in the placebo group; moderate lymphedema: 15 in the CYCLO 3 FORT group and 18 in the placebo group), arm circumference differences on D0 between the CYCLO 3 FORT group and the placebo group.

*Drop-outs*

Two of the 57 patients included in the trial were lost to follow-up for unknown reasons (1 patient in each group). Seven other patients dropped out of the trial for various reasons. In the CYCLO 3 FORT group, there were 3 drop-outs (2 for adverse side effects, 1 for poor compliance), whereas in the placebo

**TABLE 4**
**Overall (Mild and Moderate Lymphedema)**
**Reduction of Edema After CYCLO 3 FORT**

| | D30 (%) | D60 (%) | D90 (%) |
|---|---|---|---|
| Upper arm | -00.08 | -06.37 | -11.18 |
| Forearm | -02.13 | -10.50 | -14.47 |
| Whole upper arm | -01.16 | -08.50 | -12.90 |

D=day

**TABLE 5**
**Patient Self-Assessment of Functional Symptoms**
**(Visual Analogue Scale)**

| Patient Group | Texture | D90 (%) |
|---|---|---|
| **CYCLO 3 FORT** | Softness | +11.56* |
| | Heaviness | +32.78** |
| | Mobility | +33.62*** |
| **PLACEBO** | Softness | -05.07 |
| | Heaviness | +05.26 |
| | Mobility | -01.93 |

*CYCLO 3 FORT drug>placebo p=0.01; **CYCLO 3 FORT>placebo p=0.02; ***CYCLO 3 FORT>placebo p<.01; D=day

**TABLE 6**
**Subjective Assessment of Arm Quality (Patient and Investigator) on Day 90**

| Patient Group | Arm (quality) | Patient (%) | Investigator (%) |
|---|---|---|---|
| **CYCLO 3 FORT** | Improvement | 69.50 | 73.90 |
| | No change | 26.10 | 26.10 |
| | Deterioration | 04.30 | 00.00 |
| **PLACEBO** | Improvement | 32.00 | 20.00 |
| | No change | 60.00 | 60.00 |
| | Deterioration | 08.00 | 20.00 |

On D90, the efficacy in the CYCLO 3 FORT group was superior to that in the placebo group (p=0.05)

group there were 4 drop-outs (2 for lymphangitis, 2 for poor compliance).

*EFFICACY OF TREATMENT*

*Edema Reduction*

As shown in *Table 1*, the reduction in edema was significantly greater with CYCLO 3 FORT by the second month of follow-up and the difference persisted by D90 (p=0.009). In the placebo group, in contrast, edema, which showed a slight tendency to regress during the first month, actually increased in volume during the second and third months.

Volume reduction with CYCLO 3 FORT appeared to be slightly greater in the forearm than in the arms *(Tables 2-4)* although a marked improvement in edema was seen in the upper arm at D90 in patients with mild lymphedema (-23.34%). Tissue changes in these lymphedematous arms displayed a wide range of appearances according to site. Thus, apart from water and protein retention, tissue changes included fibrosis and fat deposition (as previously demonstrated in lymphedema of the lower extremities) (11). Clinically, the lymphedematous upper arm appeared to contain more fat than water in some patients whereas these proportions (fat/fluid) appeared to be reversed in the forearm. Further studies are necessary to confirm (or refute) whether the reduction in the volume of edema obtained in response to treatment is greater in the forearm and whether this response relates to the specific mechanism of action of CYCLO 3 FORT (greater effect on fluid reduction as opposed to fat reduction).

Patients with mild lymphedema appeared to obtain a greater percent reduction in edema volume than those with moderate lymphedema. Perhaps this difference relates to tissue matrix changes between recent onset (acute) lymphedema as compared with more longstanding (chronic) lymphedema.

As shown in *Table 5*, interpretation of the visual analogue scales (subjective assessment by patients), suggested that CYCLO 3 FORT was again superior to placebo and D90. The overall efficacy of CYCLO 3 FORT was apparent by the end of the second month of treatment and was statistically significant at D90 *(Table 6)*. Body Mass Index remained virtually unchanged throughout the study in both groups.

*Side Effects*

Two episodes of acute infection (lymphangitis) were observed in the placebo group leading to discontinuation of these patients in the clinical trial. Two patients in the CYCLO 3 FORT were withdrawn from the trial on D30 and D60 because of adverse side effects, namely nausea and abdominal pain. Overall, safety was rated as excellent (range 88.9-100%) by both the patients and by the investigator in both CYCLO 3 FORT and placebo groups.

*DISCUSSION*

In a controlled double-blind study conducted in two parallel groups in a total population of 57 women with lymphedema of the upper limb secondary to radiotherapy or surgery, the test drug, CYCLO 3 FORT, an extract of Ruscus Aculeatus plus Hesperidin Methyl Chalcone, significantly reduced the volume of edema when compared to a placebo. It is reemphasized that before inclusion in the study and throughout the duration of the clinical trial period of 3 months, the patients did not receive other treatment apart from manual lymphatic drainage which had already been administered for at least 30 days at the same weekly frequency and without modification during the study period.

The principal difficulty encountered was the duration of the trial (3 months) which allowed the inclusion only of outpatients, treated by different physiotherapy teams. We therefore tried to ensure that the various clinical teams applied the same techniques

and that each team managed sufficient number of patients in each group to avoid a subtle bias other than an effect from the test drug versus placebo.

This first controlled clinical trial conducted with CYCLO 3 FORT for secondary lymphedema of the arm demonstrated a clear efficacy of this drug, although the reduction in the volume of edema tended to be less than that reportedly achieved by intensive complex physiotherapy (manual compression, bandage wrapping, remedial physical exercises) (1).

Whereas the mechanism of action of CYCLO 3 FORT was not addressed, the greater reduction in the swollen forearm as contrasted with the upper arm suggests its favorable effect is greater on the liquid component rather than on surplus fat deposition. Perhaps functional lymphatic vessels and/or modification of tissue matrix by proteolytic activity of tissue macrophages play a role in CYCLO 3 FORT's beneficial action.

*REFERENCES*


1. Földi, M: Treatment of lymphedema. Lymphology 27 (1994), 1-5.
2. Lauressergues, H, P Vilain: Pharmacological activities of Ruscus extract on venous smooth muscle. Inter. Angio. 3 (1984), 70-73.
3. Marcelon, G, PM Vanhoutte: Venotonic effect of Ruscus under variable temperature conditions in vitro. Phlebology 3 (Suppl 1)(1988), 51-54.
4. Tarayre, JP, H Lauressergues: Etude de quelques propriétés phamacologiques d'une association vasculotrope. Ann. Pharma. Françaises 34 (1976), 9-10, 375-382.
5. Bouskela, E, FZG Cyrino, et al: Inhibitory effect of the Ruscus extract and of the Flavanoid Hesperidine Methylchalcone on increased microvascular permeability induced by various agents in the hamster cheeck pouch. J. Cardiovasc. Pharm. 22 (1993), 225-230.
6. Pouget, G, L Ducros, G Marcelon: Effect of Ruscus extract on peripheral lymphatic vessel pressure and flow. In: *Return Circulation and Norepinephrine: An Update*, Vanhoutte, PM (Ed.), John Libbey Eurotext, Paris, London, 1990.
7. Marcelon, G, G Pouget, et al: Effect of Ruscus on the adrenoreceptors of the canine lymphatic thoracic duct. Phlebology 3 (Suppl. 1)(1988), 109-112.
8. McHale, NG: Mechanism of noradrenaline action in lymphatic vessels. In: *Return Circulation and Norepinephrine: An Update*, Vanhoutte, PM (Ed.), John Libbey Eurotext, Paris, London, 1990.
9. Jimenez Cossio, JA, PJM Ortin, et al: Therapeutic effect of Ruscus extract in lymphedemas of the extremities. In: *Return Circulation and Norepinephrine: An Update*, Vanhoutte, PM (Ed.), John Libbey Eurotext, Paris, London, 1990.
10. Schumacher, HR, RJ Reinhard, WH Wetzler: The frustum sign. New Eng. J. Med. 279 (1968), 384-385.
11. Cluzan, RV, AF Alliot, et al: Cutaneous and subcutaneous changes in lymphedema analysed with high resolution MR imaging, indirect lymphography and lymphoscintigraphy. In: *Progress in Lymphology XIV*, Proceedings of the 14th Int'l. Congress of Lymphology, Witte, MH, CL Witte (Eds.), International Society of Lymphology, Zurich, Switzerland and Tucson, Arizona. Lymphology 27 (Suppl)(1994), pp. 305-308.



**Dr. Robert Cluzan, Treasurer**
**Service de Medecine**
**Fondation Cognac-Jay**
**15 rue Eugene Millon**
**75015 Paris, FRANCE**