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EFFICACY OF BN165 (GINKOR FORT) IN BREAST CANCER RELATED UPPER LIMB LYMPHEDEMA: A PRELIMINARY STUDY

R.V. Cluzan, A.P. Pecking, H. Mathiex-Fortunet, E. Léger Picherit

Hospital Cognacq-Jay (RVC), Centre René Huguenin (APP), Beaufour Ipsen Pharma (HMF,ELP), Paris, France

ABSTRACT

The purpose of this study was to determine whether BN165 (Ginkor Fort), which has been reported to alleviate symptoms of venous insufficiency, has a beneficial effect on lymphatic function or lymphedema symptoms. Using a 3-arm, double-blind, placebo-controlled design in 48 patients with upper extremity lymphedema secondary to breast cancer treatment, improvement in symptoms and signs as well as lymphoscintigraphic kinetic parameters (radiocolloid half-life and lymphatic migration speed) was assessed in response to treatment. A statistically significant effect on limb heaviness was noted. Lymphatic migration speed also demonstrated a significant increase at a dose of 2 active capsules per day but not at the 3 capsules per day dose, but lymphatic migration speed also improved in the placebo group. These findings in mechanical lymphatic insufficiency in breast cancer-related lymphedemas can be compared to the previously published clinical amelioration by BN165 of the subjective symptoms (heavy limbs) of dynamic lymphatic insufficiency in patients with venous insufficiency. Further studies are needed to define the possible role of BN165 in treating patients with lymphedema.

Whatever conservative treatment of the breast and axilla is selected, swelling of the arms still occurs after conventional management for breast cancer in about 15% of all treated cases (estimates vary from 1-40%). Whereas the decongestive treatments already available, such as decongestive physiotherapy, compression bandaging, and surgery, an effective drug, particularly in an oral preparation, would be a useful adjunct in lymphedema management to reduce and contain the excess limb volume in these high-molecular weight proteinaceous edemas (1). However, the number of chemical substances known to enhance lymphatic function that also might be suitable for human use is limited.

BN165 is a combination of several compounds related to the gamma benzopyrones, which have been reported to exert a direct beneficial "lymphotonic" effect on the lymphatic channels and also to enhance the activity of the macrophages, both postulated mechanisms of action directed at the underlying pathophysiology of mechanical lymphatic insufficiency. At a daily dose of 2 capsules, BN165 has been reported in clinical practice to improve venous tone, capillary permeability and resistance. The findings of two double-blind, placebo-controlled studies (2,3) have suggested that BN165 may have lymphokinetic activity (4,5).

To further explore BN165's possible beneficial effect on lymphedema symptoms and signs and lymphatic function, this comparative placebo-controlled study was designed and carried out in patients with breast cancer-related upper limb lymphedema.

MATERIALS AND METHODS

Drug Formulation

BN165 (Ginkor Fort) (Beaufort Ipsen Pharma, France) is a combination of:

1. Extract of Ginkgo biloba — 14mg [including Flavonoids (such as coumarin esters Quercetin and Kaempferol, proanthocyanidins and flavones) and Terpenes (such as Ginkgolides, Bilobalides)]
2. Troxerutin (trihydroxyethylrutoside) — 300mg
3. Heptaminol (hydrochloride) — 300mg

Patients

50 patients between 39 and 80 years of age (median 59.4 ± 2 years) were selected from the authors' (RC, AP) practice, and 48 patients were included in the trial. All patients presented with upper limb lymphedema secondary to a breast cancer treatment. Patients all had a history of cancer operations from 6 months to 31 years prior and a confirmed lymphedema of at least 3 months duration. The stage of lymphedema was not documented. Patients undergoing conventional decongestive therapy were eligible for the study on condition that this treatment would not be modified (elastic compression-manual lymphatic drainage) during the trial.

Trial Design

A three-arm, double blind, placebo-controlled trial of 2 different dose regimens of BN165 was conducted following approval by the Regional Ethics Committee (Saint-Germain en Laye, France). All patients gave their written informed consent. Patients were randomly assigned to 3 groups: 15 patients to a BN165 - 2 active capsules group (2A), 16 patients to a BN165 - 3 active capsules group (3A), and 17 patients to the placebo group (P). Each patient took 2 similar appearing capsules in the morning and 1 in the evening for 2 months. No significant differences were observed between the groups at the time of entry into the study.

Inclusion criteria: Stable lymphedema symptoms and signs for at least 3 months with previously experienced partial improvement after initial decongestive therapy.

Exclusion criteria: History of progressive cancer or any abnormality of the contralateral limb; venous thrombosis or lymphangitis or an infectious episode within the previous 30 days or more than 2 such episodes within the past year; excessive fat deposition (determined by dual X-ray absorptiometry) or overweight (BMI > 32); treatment with drugs that could interfere with the study within 30 days or treatment by pressotherapy or inelastic compressive bandages.

Clinical Evaluation:

Symptoms of discomfort (heaviness, tightness, stiff movements) were assessed by the patient on a visual analog scale (VAS). Serial perimeter measurements were performed every 5 cm and used to calculate the volume of the upper limb by summing successive truncated cone volumes. These evaluations were performed before inclusion (baseline evaluation), at day 28 (interim visit), and at day 56 (final visit).

Functional Evaluation

An indirect, functional dynamic lymphoscintigraphy using rhenium sulfocolloid labeled with technetium 99m was performed twice, once before inclusion and again at the end of the trial. The radiocolloid was subcutaneously injected bilaterally into the first web space of the hand in a small calibrated volume (0.2 ml, 18.5 MBq). The following lymphoscintigraphic parameters were recorded: lymphatic migration speed (cm/min) and the half-life (min) of the radiocolloid at the injection sites (7).

TABLE 1
Efficacy of BN165 in Upper Limb Lymphedemas. Comparison of Results Obtained at Days 0 and 56 at Doses of 2 (Group 2A) or 3 (Group 3A) Active Capsules Versus a Placebo-controlled Group. The Lymphoscintigraphic and Volumetric Results Are Expressed as the Median of the Percent Difference, and Those for the Symptoms as the Median of the Score on the Visual Analog Scale (VAS).

	Placebo Group	Group 2A	Group 3A
Scintigraphy			
Half-life	-2.97% ns	-3.72% ns	-2.04% ns
Lymphatic migration speed	+1.93% p=0.0129	+3.29% p=0.0103	-1.63% ns
Volumetry	+1.16% ns	-1.24% ns	+0.96% ns
Symptoms			
Heaviness (VAS mm)	6 ns	16 p=0.0175	2 ns
Tightness (VAS mm)	9.5 p=0.0178	11 p=0.0129	2 ns
Stiff movement (VAS mm)	1 p=0.0464	18 p=0.0038	10.5 p=0.056
Quality of life SF36	No change	No change	No change

Study Objectives

The primary end point was a lymphokinetic effect of BN165 in the lymphedematous arm and on the normal contralateral limb in terms of improved functional dynamic lymphoscintigraphic parameters (half-life of tracer and lymphatic migration speed). The secondary objectives were: assessment of a dose-effect response comparing the 2- versus 3-capsule regimen; efficacy on swelling (differences between the calculated volumes of the affected and contralateral limbs); and efficacy on the symptoms (VAS for heaviness, tightness, stiff movements). The other parameters investigated were the effect on quality of life using the SF36 scale, safety and global efficacy based on the patient assessment.

Statistical Analysis

The comparability of groups at the inclusion was assessed using a Chi-square test (or a Fischer's exact test, depending on the sample size) and a student's t-test for independent samples. The change over time in the two groups was compared using a two-way analysis of variance (group x time) with repeated measurements of time. If the group x time interaction was found to be significant, a complementary analysis was performed to investigate the group effect. The significance was set at $p \leq 0.05$ for all analyses.

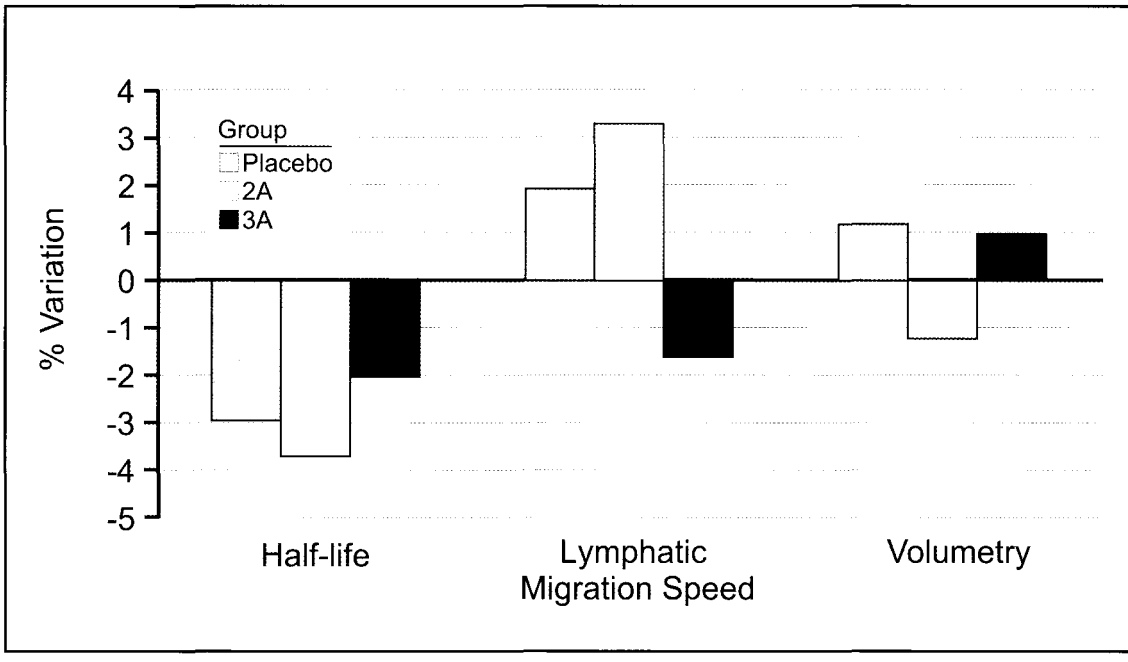

Fig. 1. Diagram comparing the results obtained for lymphoscintigraphic parameters (radiocolloid half-life and lymphatic migration speed) and volumetry at days 0 and 56. The lymphatic migration speed results obtained for group 2A (and placebo) are significantly better at day 56 (NS when compared to each other).

Calculations were performed using SAS 6.12 release on a TSO20 (AIX) computer.

RESULTS

The purpose of this study was to determine whether BN165 had a beneficial effect compared to placebo on symptoms and signs and well as lymphokinetics in patients with lymphedema after breast cancer treatment. During the trial, there were no dropouts from the patient groups. Both BN165 and the placebo were well-tolerated without adverse side-effects.

The findings are summarized in *Table 1.* The primary endpoint, a lymphokinetic action of BN165, was assessed by lympho-scintigraphic parameters on day 56 compared to the baseline evaluation. Data were expressed as the median of the percentage change after finding that raw data was not in normal distributions. No significant difference was observed for the radiocolloid half-life [group P: -2.97% (NS) — group 2A: -3.72% (NS) — group 3A: -2.04% (NS)]. Lymphatic migration speed was increased for Group 2A but also for P [group P: 1.93% (p=0.013) — group 2A: 3.29% (p=0.010) (NS cf. P) — group 3A: -1.63% (NS)]. Insignificant differences were found in all groups for volumetry [group P: +1.16% (NS) — group 2A: -1.24% (NS) — group 3A: +0.96% (NS)]. Reduction in heaviness was found only in Group 2A [group P: 6 mm (NS) — group 2A: 16 mm (p=0.017) — group 3A: 2 mm (NS)]; tightness in both groups P and 2A [group P: 9.5 mm (p=0.017) — group 2A: 11 mm (p=0.012) — group 3A: 2 mm (NS)] and stiff movements in all groups [group P: 1 mm (p=0.046) — group 2A: 18 mm (p=0.003) — group 3A: 10.5 mm (p=0.05)]. Nonetheless, a trend for better results was consistently obtained for group 2A than for the group receiving 3 capsules or the group receiving the placebo *(Fig. 1).*

Day 0	Affected Arm	Contralateral Arm
T1/2 (min)	217.27	120.32
LS (cm/min)	8.103	8.125
Day 56		
T1/2 (min)	190.27	121.71
LS (cm/min)	8.667	9.003

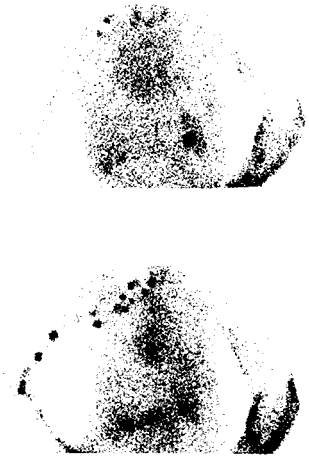

Fig. 2. Lymphoscintigraphic results at days 0 and 56 for a patient (#65) receiving 2 active capsules. On day 56, there is less lymphostasis of the affected (left) arm (reduction in total radiocolloid count). There are more functional nodes in the contralateral (right) arm. The half-life and lymphatic migration speed also improved at the day 56 time point. LS: lymphatic migration speed. T1/2: half-life of radiocolloid.

A lymphokinetic action of BN165 was suggested in the morphological lymphoscintigraphic results: patients receiving 2 active capsules displayed less lymphostasis in the swollen limb and a significant improvement in the lymphatic drainage of the contralateral limb, with more functional nodes *(Fig. 2).* The half-life and lymphatic migration speed were improved in this patient.

No significant change was observed in the quality of life (SF36) despite subjective improvement in symptoms regularly observed in the group receiving 2 active capsules.

DISCUSSION

This study suggested a beneficial effect of BN165 (Ginkor Fort) on lymphedema symptoms of limb heaviness and possibly on lymphatic function in patients with upper extremity lymphedema after breast cancer treatment. In the literature, there are two other trials that also suggest that this compound affects the lymphatic system. Thibault (5), using the inguinal uptake of technetium-labeled Rhenium sulfide in humans demonstrated that Ginkor Fort was able to increase the inguinal uptake both at rest and after exercise. Lagrue and Behar (4), using the Isotopic Landis Test, demonstrated that in orthostatic idiopathic edema, Ginkor Fort not only restored normal capillary permeability but also normalized the ratio of low to high frequency lymphatic oscillations, suggesting a positive impact on lymphatic function.

At the 2-capsule dose, BN165 was consistently more effective than the 3-capsule dose. Subjective symptoms improved particularly the feeling of heaviness. The lack of dose response proportionality (no statistical efficacy with the 3 active capsules per day in contrast to the effect of 2 active capsules) remains to be explained. This phenomenon has also been reported for other drugs in different clinical settings.

From the practical standpoint, it is clear that further trials are needed to confirm the efficacy of BN165 in lymphedema treatment, although this preliminary study suggests

some clinical efficacy but also a placebo effect. Such efficacy in relieving symptoms of impaired venous return, notably the subjective feeling of heaviness, could be related to the lymphokinetic effect in mechanical lymphatic insufficiency within the limitations of the lymphokinetic parameters studied. It is well known that in dynamic lymphatic insufficiency, lymphatic functional capacity is at its peak, the lymphatic load exceeding the functional capacity of the lymphatic system. Nevertheless, Taylor (7) demonstrated under experimental conditions that following damage to the endothelium, the function of this system can be increased slightly. We could ask: would it be possible to obtain the same type of increased functional capacity using drugs?

CONCLUSIONS

BN165 (Ginkor Fort) is well-tolerated, without side effects, and relieves limb heaviness in patients with breast cancer-related lymphedema. Further controlled clinical trials are required to demonstrate that it could be useful for the treatment of lymphedema. One interesting possibility is that substances of this type might be able to boost lymphatic function above the theoretical maximum, which is the challenge in dynamic lymphatic insufficiency. Further research is needed to explore this point.

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Robert V. Cluzan, MD
Le Clos de l'Aumône Malnoue
7 Avenue Charles Bras
77184 Emerainville, FRANCE
Telephone: 33-1-64 61 77 54
e-mail: malnoue@chello.fr