

## Venous Leg Ulcer: A Meta-analysis of Adjunctive Therapy with Micronized Purified Flavonoid Fraction

P. Coleridge-Smith,<sup>1</sup> C. Lok<sup>2\*</sup> and A.-A. Ramelet<sup>3</sup>

<sup>1</sup>Department of Surgery, UCL Medical School, The Middlesex Hospital, London WIN 8AA, UK; <sup>2</sup>CHU, Service de Dermatologie, Hopital Sud, 80054 Amiens Cedex 1, France; and <sup>3</sup>2 Place Benjamin Constant, 1003 Lausanne, Switzerland

**Objective.** To assess the effect of oral treatment with micronized purified flavonoid fraction (MPFF) on leg ulcer healing.

**Design.** Meta-analysis of randomised prospective studies using MPFF in addition to conventional treatment.

**Materials and methods.** Five prospective, randomised, controlled studies in which 723 patients with venous ulcers were treated between 1996 and 2001 were identified. Conventional treatment (compression and local care) in addition to MPFF was compared to conventional treatment plus placebo in two studies (N=309), or with conventional treatment alone in three studies (N=414). The primary end point was complete ulcer healing at 6 months.

**Results.** At 6 months, the chance of healing ulcer was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone (RRR: 32%; CI, 3–70%). This difference was present from month 2 (RRR: 44%; CI, 7–94%), and was associated with a shorter time to healing (16 versus 21 weeks; P=0.0034). The main benefit of MPFF was present in the subgroup of ulcers between 5 and 10 cm<sup>2</sup> in area (RRR: 40%; CI, 6–87%), and those present for 6–12 months duration (RRR: 44%; CI, 6–97%).

**Conclusion.** These results confirm that venous ulcer healing is accelerated by MPFF treatment. MPFF might be a useful adjunct to conventional therapy in large and long standing ulcers.

**Keywords:** Bandages; Compression therapy; Varicose ulcer; Meta-analysis; Flavonoids; Micronized purified flavonoid fraction (MPFF).

### Introduction

Leg ulcers are mostly of venous origin.<sup>1</sup> The standard of care for venous leg ulcers is based on local wound care and application of compression therapy.<sup>2</sup> Published rates of healing utilizing this standard of care vary widely between 45%<sup>3</sup> and 83%<sup>4</sup> with 24 weeks of treatment. In addition, the medical costs associated with the long-term care of these chronic wounds are substantial.<sup>1,2</sup> These difficulties in ulcer management has raised interest in pharmacological treatment to promote healing. Selecting an appropriate medication requires an understanding of the pathological causes leading to leg ulceration. It has been shown that inappropriate leucocyte activation is present in chronic venous disease and that this may be important as a cause of venous ulceration.

Micronized purified flavonoid fraction (MPFF, Daflon 500 mg<sup>®\*</sup>, Servier, France), consisting of 90% diosmin and 10% flavonoids expressed as hesperidin, has been shown to protect the microcirculation from damage secondary to raised ambulatory venous pressure.<sup>5</sup> It decreases the interaction between leucocytes and endothelial cells by inhibiting expression of endothelial intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule (VCAM), as well as the surface expression of some leucocyte adhesion molecules (monocyte or neutrophil CD 62 L, CD11B).<sup>6</sup> There are few known side effects, and interactions with other drugs have not been reported.<sup>5</sup> In previous trials,<sup>5</sup> MPFF used as adjunctive therapy to compression and appropriate local care demonstrated promising results on the acceleration of the healing process. The objective of this meta-analysis was to quantify the specific effect of MPFF over conventional treatment in venous leg ulcer healing. An additional objective of this analysis was to investigate those clinical situations in which adjunctive MPFF might be more appropriate.

\*Corresponding author. Dr Catherine Lok, MD, PhD, Service de Dermatologie, Hopital Sud, 80054 Amiens Cedex 1, France.

E-mail address: lok.catherine@chu-amiens.fr

\*Also registered as Ardiun<sup>®</sup>, Alvenor<sup>®</sup>, Arvenum<sup>®</sup> 500, Capiven<sup>®</sup>, Detralex<sup>®</sup>, Elatec<sup>®</sup>, Flebotropin<sup>®</sup>, Variton<sup>®</sup>, Venitol<sup>®</sup>.

## Materials and Methods

### *Search*

Electronic databases were searched, including Medline, Embase, and the Cochrane Library (last search December 2003). All randomised controlled trials examining the effect of compression alone *versus* adjunctive treatment on the healing of venous leg ulcer were considered, with no restriction on publication status, date or language.

### *Study selection*

Controlled trials of venous leg ulcer healing were selected with the key words Daflon 500 mg, MPFF, or flavonoids. The analysis in this report was limited to investigations with (1) randomised, controlled study design; (2) inclusion and exclusion criteria clearly described; (3) an accurate diagnosis of the venous origin of the ulcer; (4) objective criteria used for the end-point assessment; and (5) treatments prescribed at the manufacturer's recommended dose for MPFF (two tablets per day). Patients included in these trials had clinical signs of venous leg ulceration such as hyperpigmentation, lipodermatosclerosis, and an ulcer located in the gaiter region. They also had a previous history of varicose veins or post-thrombotic syndrome. Patients were investigated by either continuous wave venous Doppler or by duplex ultrasound examination at baseline to confirm the presence of venous reflux. Reflux duration of  $>0.5$  s was taken as evidence of venous valve incompetence. In addition, continuous wave Doppler or duplex ultrasound examination was used to exclude patients with arterial diseases (ankle brachial index  $>0.8$ ). The duration of the current ulcer had to be at least 3 months for inclusion in these trials.

All patients were treated with conventional therapy combining compression and appropriate local care. MPFF was given as an adjunctive therapy in all trials. A minimum compression of 30 mmHg at the ankle was accepted as appropriate for the management of leg ulcers. Decisions over inclusion of studies were made according to predefined items of a checklist for methodological quality recommended by the Cochrane Wounds Group (see below).

### *Definition of the meta-analysis end points*

Complete ulcer healing after 6 months of treatment was the main end point of the meta-analysis. Complete

healing is the most common end point used.<sup>7</sup> It was defined as complete wound re-epithelialisation. We chose a 6-month treatment period as this is the duration of treatment recommended in consensus documents on venous ulcers,<sup>7,8</sup> and is frequently used for randomised controlled trials for leg ulcers. In patients with multiple ulcers, the reference ulcer was that with the largest area.

The secondary end points of this study were time to healing, as well as the healing rate at intermediate times (2 and 4 months), and the healing rate according to ulcer characteristics.

### *Definition of subgroups of patients*

The patient database was made available to us by the manufacturer so that we could stratify analyses according to the ulcer characteristics of the patients. This was done according to the prognostic model previously used to screen patients with a venous leg ulcer likely to remain unhealed within 24 weeks.<sup>9</sup> In validation data sets, ulcers with a high risk of failure to heal were those larger than 5 cm<sup>2</sup> and those that had been present for more than 6 months. Subgroups were, therefore, defined according to (i) the ulcer size:  $<5$ , 5–10,  $\geq 10$  cm<sup>2</sup>; and  $<10$  and  $\geq 10$  cm in the long axis, (ii) the ulcer duration:  $<6$  months, 6–12 months, and  $\geq 12$  months); and (iii) the time from first ulcer, defined as the period of time since the onset of the first ulcer to the time of each trial. This was divided into patient with duration of disease  $<5$  years or  $\geq 5$  years.

### *Statistical analysis*

The reduction of the relative risk (RRR) and 95% confidence interval (CI) were calculated for healing rate for the MPFF treatment group compared to the standard treatment group. Type 1 error was set at 5%. Since, the desired treatment effect is increased ulcer healing, RRR expresses a better chance of an ulcer healing and, therefore, should be positive to indicate a benefit of adjunctive MPFF over conventional treatment alone. We did not use an odds ratio calculation because such calculations are difficult to interpret clinically. Data were combined by applying the standard methodology outlined by Whitehead and Whitehead.<sup>10</sup> Assessment of homogeneity between trials was performed using Cochran *Q* test.<sup>11</sup> Heterogeneity was judged significant if the *P* value was less than 0.05. Where there was non-homogeneity between trials, a random effect model was used.<sup>11</sup> The overall

estimated relative risk (RR) was the result of an exponential transformation of the maximum likelihood estimator (MLE) obtained with the model. In other situations, a fixed effect model was used, and results were confirmed with a random effect model.<sup>11</sup> In cases of heterogeneity, sensitivity was assessed to determine the effect of sources of variation. The standard Kaplan–Meier methodology was used to estimate the probability of healing over time,<sup>10</sup> and homogeneity of the log hazard ratios between trials was performed using the Cochran Q test.<sup>11</sup> The common hazard ratio was estimated and tested using the Peto method.<sup>11</sup>

#### *Data management*

Information was sought from either the investigators or the manufacturer. Patient databases were received in an electronic format and extracted for the analysis by an independent company (IDDI, Brussels, Belgium). The authors acknowledge that this meta-analysis was funded by the manufacturer of MPFF but consider that the use of an independent data management company distances the funding of the study from the objective data analysis. The data reported here can be considered as reliable as any study in which data have been aggregated from a number of different controlled trials.

### **Results**

#### *Description of selected trials (Tables 1 and 2)*

A total of 15 publications on MPFF in ulcer healing were identified by the literature search, of which three were controlled trials.<sup>12–14</sup> Four additional unpublished controlled trials were obtained from the manufacturer's files.<sup>15–18</sup> Seven studies were identified that met the methodological characteristics required by the Cochrane Wounds Group (Table 1): in each trial, inclusion and exclusion criteria were well defined, the method used for the randomisation was mentioned, treatment groups were comparable at baseline for age, gender, and ulcer characteristics. Reference ulcers were assessed at baseline by their longest axis (cm) or by planimetry (cm<sup>2</sup>); sample size had been calculated a priori in some trials,<sup>15–18</sup> and the number of patients was over 100 in all trials. Of these studies, four had used blinded assessment of ulcers.<sup>12,15–17</sup> Planimetry assessments had not been reported at intermediate study times in one study.<sup>17</sup> In

another study,<sup>16</sup> 7% of ulcer data was found to be missing at baseline, 12.8% of patients displayed major deviations from the protocol, and 25.4% had been withdrawn or lost to follow-up. These two trials<sup>16,17</sup> were, therefore, excluded, so that five studies were finally selected<sup>12–15,18</sup> as relevant randomised controlled trials (RCT), two of which are unpublished.<sup>15,18</sup>

Descriptive data of each of the five selected trials (RCT1 to RCT5) are shown in Table 2.

All five trials had a similar design in that the MPFF group was compared to a control group. In the MPFF group, the medication was given at the currently recommended dose (2 × 500 mg MPFF per day) for 2 months in RCT1<sup>12</sup> or 6 months in the others,<sup>13–15,18</sup> in combination with conventional therapy. In RCT1<sup>12</sup> and RCT2<sup>15</sup> patients, the control group received placebo at the same dose in addition to conventional therapy. In the three other trials,<sup>13,14,18</sup> control subjects received conventional treatment alone. Local treatment consisted of mechanical cleaning,<sup>12–15,18</sup> application of normal saline and moist pads.<sup>12–15,18</sup> Local treatment varied to some extent depending on the country of the study: hydrocolloid dressings were used in France, Germany, and Poland,<sup>12,13,15</sup> and silver nitrate solution was used in Czech Republic,<sup>14</sup> while silver sulfadiazine and paraffin were used in Russia.<sup>18</sup> Compression was applied to the limbs of all patients using stockings or bandages to achieve a minimum of 30 mmHg compression. In RCT2,<sup>15</sup> inelastic bandages were used so that the pressure applied reached 40 mmHg at the ankle (Table 2).

In one study (RCT5),<sup>18</sup> the time to healing was the primary outcome measure while in the remaining studies the percentage of patients with complete ulcer healing was used.<sup>12–15</sup> The treatment protocol was re-evaluated regularly, with assessments carried out every 2 weeks until month 2 in RCT1,<sup>12</sup> or month 3 in RCT2–4<sup>13–15</sup> and then monthly until month 6.<sup>13–15</sup> Only in one trial (RCT5)<sup>18</sup> were visits scheduled monthly. Compliance with treatment was evaluated during these visits. Compliance with oral treatment was considered as satisfactory if 80% of the theoretical dosage had been taken. Patients who attended wearing their stockings or with bandages correctly applied as assessed by the investigators were considered as compliant with compression. Reported compliance to oral treatment varied between 90 and 99% (Table 3). Compliance with compression was reported in two studies.<sup>15–18</sup> It was 88% in each group in RCT2<sup>15</sup> and two patients (one in each group) deviated from the protocol for compression in RCT5.<sup>18</sup> All studies were analysed on an intention-to-treat basis.

**Table 1. Randomised controlled trials of micronized purified flavonoid fraction (MPFF) used in combination with conventional treatment for the healing of venous leg ulcers**

Trial (date of publication)	Inclusion and exclusion criteria	Sample size (arms)	A priori sample size calculation	Method of randomization	Baseline comparability of treatment groups	Masking	Appropriate outcome measures	Intention-to-treat analysis
RCT1: Guilhou and colleagues <sup>12</sup> (1997)	Yes	107 (2)	Not stated	Stratified randomization according to the initial ulcer size	Yes	Double	Yes, planimetry	Yes
RCT2*: Rieger/Zuccarelli <sup>15</sup>	Yes	202 (2)	Yes	Sealed envelopes	Yes	Double	Yes, planimetry	Yes
RCT3: Glinski and colleagues <sup>13</sup> (1999)	Yes	140 (2)	Not stated	Central randomization list	Yes	No	Yes, planimetry	Yes
RCT4: Roztocil and colleagues <sup>14</sup> (2003)	Yes	150 (2)	Not stated	Not stated	Yes, except male predominance in the control group	No	Yes, planimetry	Yes
RCT5*: Saveliev and colleagues <sup>18</sup>	Yes	124 (2)	No	Central randomization list	Mean initial ulcer area larger in the control group, but comparable median size and length in both groups	No	Yes, planimetry	Yes
RCT6*: Ming Keng and colleagues <sup>16</sup>	Yes	134 (2)	Yes	Central randomization list	Not stated	Double	Yes	Yes
RCT7: Ulloa and colleagues <sup>17</sup>	Yes	137 (2)	Yes	Sealed envelopes	Yes	Double	Yes	Yes

RCT, randomised controlled trial.

\* Trials without a date of publication are unpublished.

**Table 2. Summary of the five trials that met the inclusion criteria**

Trial	Diagnostic method	Intervention	Control	Outcome
Guilhou and colleagues <sup>12</sup> (RCT1)	Clinical examination and A-V Doppler-assessed ABI >0.8 and ulcer duration >3 months	MPFF 500 mg, two tablets per day plus elastic compression	Placebo plus elastic compression	Complete healing of the reference ulcer (complete re-epithelialisation) at 2 months and lifetime analysis
Rieger/Zuccarelli <sup>15</sup> (RCT2)	Clinical examination and duplex-determined venous reflux (ABI >0.9) and ulcer duration >3 months	MPFF 500 mg, two tablets per day plus inelastic two-layer compression, or biflex	Placebo plus inelastic two-layer compression, or elastic compression	Complete healing of the reference ulcer (i.e. re-epithelialisation) at each consultation (weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24) and survival analysis
Glinski and colleagues <sup>13</sup> (RCT3)	Clinical examination and Doppler flowmetry (ABI >0.9) and ulcer duration >3 months	MPFF 500 mg, two tablets per day plus setopress compression bandages	Setopress compression bandages without placebo	Complete healing of the reference ulcer at each consultation (weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24)
Roztocil and colleagues <sup>14</sup> (RCT4)	Clinical examination and ABI >0.9 assessed by A-V Doppler and ulcer duration >3 months	MPFF 500 mg, two tablets per day plus elastic bandage (type not specified)	Elastic bandage without placebo	Complete healing of the reference ulcer at each consultation (weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24) and time to complete healing
Saveliev and colleagues <sup>18</sup> (RCT5)	Clinical examination and ABI >0.8 assessed by A-V Doppler and ulcer duration >3 months	MPFF 500 mg, two tablets per day plus elastic compression (type not specified)	Elastic bandage without placebo	Time to complete healing, rate of patients with complete healing at 6 months

Trials 15 and 18 are unpublished; ABI, ankle-brachial index; A-V Doppler, continuous wave Doppler ultrasound; MPFF, micronized purified flavonoid fraction; RCT, randomised controlled trial.

### Patient characteristics at baseline in selected trials (Table 3)

#### Demographics

The average age of the population was 64.7 years (range: 20–88 years), with a higher proportion of women than men (58 *versus* 42%).

#### Description of patients according to the CEAP classification

All patients included in these studies were in CEAP clinical class C6 from the definition of the entry criteria. The clinical trials in this meta-analysis did not include sufficiently detailed investigation with duplex ultrasonography to be able to report the E, A and P of CEAP. Duplex ultrasonography was not universally available at all centres when the study protocols were designed and the CEAP classification was not universally implemented at the time.

#### Ulcer characteristics

The mean ulcer length was 4.5 cm (range: 1–14 cm) and mean ulcer area 10.4 cm<sup>2</sup> (range: 1–108 cm<sup>2</sup>). The mean duration of current ulcer was 19.6 months (range: 1–237 months). The average number of ulcers at inclusion was 1.6.

#### Duration of the ulcer disease

When entering the trials, the patients in this meta-analysis had had their first ulcer on average 13.5 years previously (range: 0–58 years).

#### Location of ulcer and reflux

Forty-four percent of patients had bilateral leg ulcers, one third (32%) had ulcers located on the left limb only, and 24% on the right leg only. Location of reflux was reported in 57% of the sample. Of those patients, 39% had superficial reflux alone, 21% had deep reflux alone, and 34% had both a superficial and deep venous abnormalities. In the remaining 6%, the location of reflux was defined as 'other'.

For all criteria described above, both groups were comparable at baseline.

#### Previous treatments (Table 3)

Between 7 and 62.3% of patients had undergone previous surgery by stripping of the saphenous veins or by phlebectomy. Sclerotherapy had been performed in 0–43.2% of patients depending on the trial.

#### Treatment effect in all patients

Results described below are summarized in Table 4.

#### Healing rates at 6 months (primary end point)

Four trials which included 616 patients continued for 6 months (RCT2–5).<sup>13–15,18</sup> At this time point, 61.3% of these patients were completely healed in the MPFF group *versus* 47.7% in the control group in the naïve pooling. When the four trials were combined, the RRR for healing was 32% (CI, 3–70%) in favour of the MPFF group. Nonetheless, heterogeneity between the groups of trials was significant ( $P=0.014$ ). The combination was sensitive to exclusion of RCT2<sup>15</sup> (RRR: 45%; CI, 23–71%). In this study,<sup>15</sup> some patients received higher compression bandages (40 mmHg instead of 30 mmHg for the rest of the sample), but exclusion from the study of patients wearing high compression had little impact on the results. On the other hand, the proportion of small ulcers (<5 cm<sup>2</sup>) was bigger in RCT2, compared with the other studies (55 *versus* 43%), as were ulcers that had been present for less than 6 months at the time of each trial (49 *versus* 34%). Heterogeneity recorded at 6 months when all trials were combined may be due to differences in ulcer characteristics in RCT2. This was verified by sensitivity tests: exclusion from the combined studies of patients with ulcers <5 cm<sup>2</sup> and of those with ulcers <6 months raised the chance of ulcer healing to 53% (CI, 15–103%) and 41% (CI, 9–81%), respectively. Estimates were homogeneous across studies.

#### Healing rates at intermediate times

Results at month 2 allowed consideration of one additional trial (RCT1).<sup>12</sup> Therefore, the chance for ulcer healing in the MPFF group compared to the controls in these five trials combined ( $N=723$ ) was 44% (CI, 7–94%;  $P=0.015$ ) and the studies were homogeneous (Fig. 1). No statistical significance was reached in the analyses at month 4 ( $P=0.07$ ).

#### Time to healing

The relative hazard of healing was 38% higher in the MPFF group compared to the control group (CI, 11–70%). The curve of the cumulative percentage of patients who had healed their ulcer over time (Fig. 2) indicates a significantly shorter time to healing in the MPFF group compared with the control group (16 *versus* 21 weeks; hazard ratio = 1.33). A strong trend in favour of MPFF began to emerge by week 8 of treatment.

#### Treatment effect in patient subgroups

##### Effect of ulcer size

Ulcers between 5 and 10 cm<sup>2</sup> ( $N=146$ ) had a 40% better chance of healing with adjunctive MPFF (RRR:

**Table 3. Demographic data in the global population and by trial**

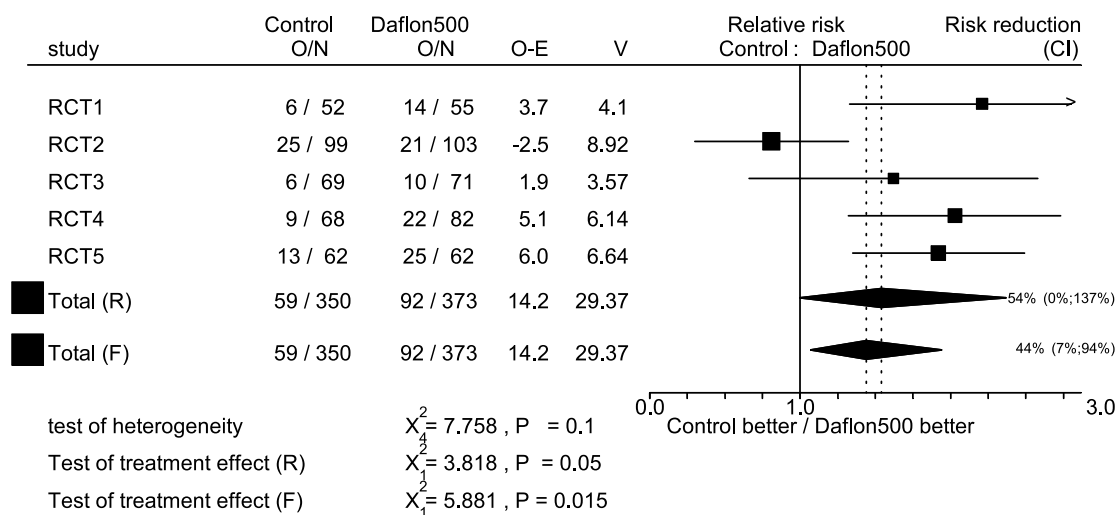
	All patients MPFF/ control (mean)	RCT1 <sup>12</sup> MPFF/ control	RCT2 <sup>15</sup> MPFF/ control	RCT3 <sup>13</sup> MPFF/ control	RCT4 <sup>14</sup> MPFF/ control	RCT5 <sup>18</sup> MPFF/ control
Age (years)	64.8/64.6 (64.7)	70.5/70.4	68.9/67.4	65.1/65.2	63.3/64.8	54.5/54.4
Gender (female in %)	60/55 (58)	76/62	66/62	26/31	77/57	52/63
BMI (kg/m <sup>2</sup> )	–	26.1/27.7	–	29/30	30/31	–
Presence of VV (%)	71/71 (71)	55/63	46/45	94/96	94/88	–
Presence of PTS (%)	41/40 (41)	55/44	52/54	4/4	51/53	–
Previous stripping or phlebectomy (%)	(30.2)	25/32.7	62.3 (global)	7/7	17.6/28	–
Previous sclerotherapy (%)	(19.3)	28.8/30.9	43.2 (global)	0/0	4.4/3.7	–
Type of reflux (%)						
Superficial	38/39 (39)	42/33	37/43	–	–	–
Deep	21/20 (21)	25/23	19/19	–	–	–
Superficial + deep	32/36 (34)	31/40	32/34	–	–	–
Localization of the disease						
Right (%)	24/24 (24)	15/20	17/21	31/26	21/23	37/29
Left (%)	32/31 (32)	31/22	33/26	34/36	20/24	47/50
Both (%)	44/45 (44)	54/59	50/53	35/38	60/53	16/21
Duration of CVD (years)	24.4/23.4 (24.0)	23.9/23.4	32.3/30.5	21.9/21.1	21.9/22.5	19/20
Time from first ulcer (years)	13.3/13.7 (13.5)	15.8/15.6	17.1/19.0	14.6/13.0	12.5/11.2	4.5/7.5
Duration of the reference ulcer (months)	17.5/21.8 (19.6)	–	12/22	29/26	17/17	11/15
Ankle/arm systolic ratio	1.1/1.1 (1.1)	1.1/1.1	1.1/1.1	1.1/1.1	1.1/1.1	1.1/1.1
Mean length of ulcer of reference (cm)	4.54/4.5 (4.5)	5.3/5.5	4.1/4.1	5.5/6.0	4.2/4.1	3.4/3.7
Mean surface of ulcer of reference (cm <sup>2</sup> )	9.7/11.2 (10.4)	18.0/19.2	7.0/7.6	12.0/15.5	9.0/8.7	4.8/8.0
Mean number of ulcers	1.6/1.6 (1.6)	1.7/1.9	1.8/1.7	–	–	1.2/1.2
Wearing of compression						
30 mmHg (%)	85/87	100/100	56/66	100/100	100/100	100/100
40 mmHg (%)	15/13	–	44/34	–	–	–
Compliance to oral treatment	–	>90%	98–99%	99%	99%	97.6%
Compliance to compression	–	–	88%/88%	–	–	2 pts with protocol deviation

Abbreviations: BMI, body mass index; CVD, chronic venous disease; MPFF, micronized purified flavonoid fraction; PTS, post-thrombotic syndrome; RCT, randomised controlled trial; VV, varicose veins; pts, patients.

**Table 4. Reduction of the relative risk of ulcer healing at 6 months in trials comparing the micronized purified flavonoid fraction (MPFF) group with the control group and percentage of ulcers healed in each group**

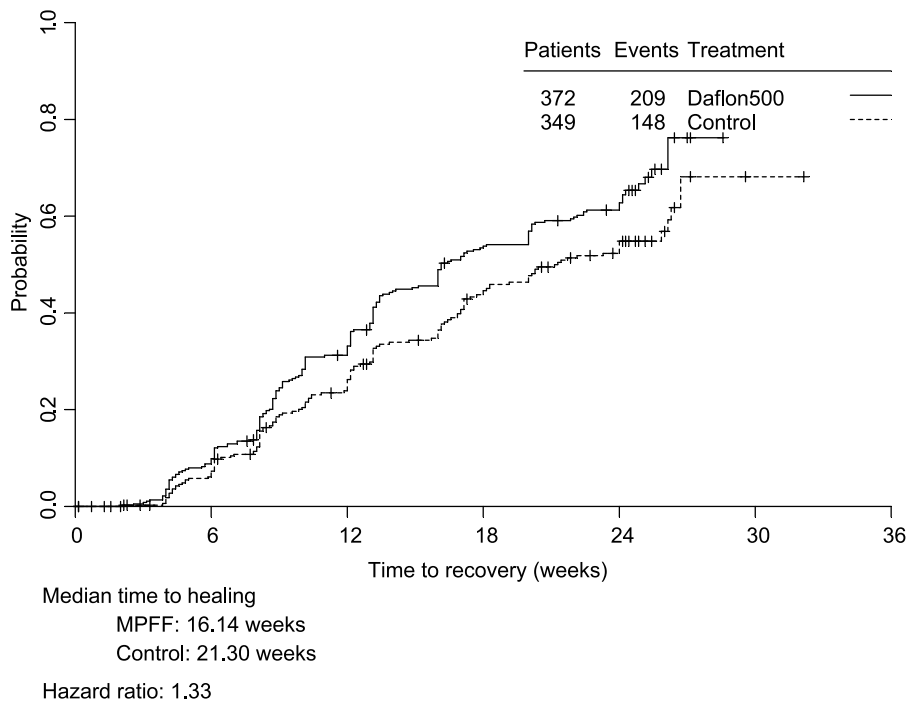
Sub-group of ulcers	Number (N) at month 6	Percentage of ulcers healed (naïve pooling) in		RRR (%)	95% CI (%)	Test of treatment effect, P value	Test of heterogeneity, P value
		Control group	MPFF group				
All ulcers	616	47.6	61.3	32	3–70	0.03	0.014
Explanation of the heterogeneity of studies							
All ulcers except those from RCT2	414	44.2	66	45	23–71	<0.001	NS
All ulcers except those with compression ≥40 mmHg in RCT2	550	48.1	62.8	31	13–71	0.047	0.016
All ulcers except those <5 cm <sup>2</sup>	319	30.3	46.9	53	15–103	0.0035	NS
All ulcers except those <6 mo	337	35.3	49.1	41	9–81	0.008	NS
According to ulcer size							
<5 cm <sup>2</sup>	297	66.4	76.6	18	(–6)–60	NS	0.016
≥10 cm <sup>2</sup>	220	20.7	33.7			NS*	NS
Between 5 and 10 cm <sup>2</sup>	146	42.6	61.5	40	6–87	0.019	NS
<10 cm <sup>2</sup>	442	58.5	71.5	25	2–54	0.035	0.026
<10 cm in long axis	609	47.6	62	33	4–69	0.021	0.021
According to ulcer duration							
<6 mo	279	62.6	75.8	23	(–6)–60	NS	0.024
≥12 mo	201	30	42	40	(–7)–109	NS	NS
Between 6 and 12 mo	136	44	59.7	44	6–97	0.021	NS
<12 mo	415	57	70	26	(–1)–62	NS	0.01
According to time from first ulcer							
<5 years	164	56	82	36	12–67	0.0023	NS

Abbreviations: mo, months; RCT, randomised controlled trial; RRR, reduction of the relative risk; CI, confidence interval; NS, non-significant. \* Based on odds ratio calculation.



O, observed number of healed patients; N, total number of patients; E, expected number of healed patients; V, variance; CI, confidence interval.

**Fig. 1.** Reduction of the relative risk of ulcer healing at 2 months in trials comparing micronized purified flavonoid fraction (MPFF) with control. O, observed number of healed patients; N, total number of patients; E, expected number of healed patients; V, variance; CI, confidence interval.



**Fig. 2.** Life-table analysis with cumulative percentage of patients in whom the ulcer healed completely. Comparison in cumulative healing rates between the micronized purified flavonoid fraction group (solid line) and the control group (broken line). Median time to healing: MPFF, 16.14 weeks; control, 21.30 weeks. Hazard ratio, 1.33.

40%; CI, 6–87%;  $P=0.019$ ). No heterogeneity was found in this subgroup. As a whole, the 609 participants with ulcers less than 10 cm in diameter ( $N=609$ ) and those with an ulcer below 10 cm<sup>2</sup> ( $N=442$ ) had, respectively, a 33% (CI, 4–69%) and 25% (CI, 2–54%) better chance of healing with adjunctive MPFF. In contrast, no significant effect of MPFF over standard treatment was shown for ulcers larger than 10 cm<sup>2</sup> or smaller than 5 cm<sup>2</sup>.

#### Effect of ulcer duration

In patients with an ulcer that had been present between 6 and 12 months ( $N=136$ ), the RRR of healing was 44% (CI, 6–97%), and studies were homogeneous. For those patients who had had an ulcer for less than 12 months ( $N=415$ ), the RRR of healing was 26% but results did not reach significance in this subgroup (CI, 1–62%;  $P=0.06$ ). No significant MPFF effect over standard treatment was found for ulcers of shorter duration (<6 months), or for the most long lasting ones ( $\geq 12$  months).

#### According to the time from first ulcer (duration of the ulcer disease)

Of the 723 participants, in 520 the duration of their ulcer disease had been recorded. A total of 164 participants had had their first ulcer episode for less than 5 years. In this subgroup of patients, the chance of

healing their ulcer at month 6 was better in the MPFF group (RRR: 36%; CI, 12–67%). In the remaining patients in whom ulcer disease had persisted for more than 5 years, results were not significant.

#### According to the location of reflux

It was not possible to establish whether patients with superficial venous reflux alone fared any better than those with a combination of deep and superficial venous reflux. The data concerning this distinction was not recorded and not reliably established in many centres involved in the studies that did not have duplex ultrasonography available to them.

#### Effect of post-thrombotic syndrome

The RRR of healing at 6 months was 47% (CI, 14–90%) in patients reporting a previous history of venous thrombosis in the lower limb ( $N=236$  at month 6), and the studies were homogeneous. Nevertheless, the presence of post-thrombotic syndrome was not systematically verified by duplex ultrasonography in these trials so these findings must be regarded cautiously.

## Discussion

This meta-analysis confirms that MPFF as adjunctive

therapy to good local wound care and compression therapy has a favourable effect on the healing process within 6 months, with a 32% better chance of patients healing the ulcer and a healing process shortened by 5 weeks. The aim of this meta-analysis was to answer a specific question concerning the value of oral MPFF treatment in the management of venous leg ulcers. The authors acknowledge that in many cases venous ulceration may be partially or totally attributable to superficial venous incompetence. Surgery to saphenous trunks and varices has been shown to be effective in the management of venous ulceration. In particular, ulcer recurrence has been prevented in patients with superficial venous insufficiency (SVI) and in those with combined segmental deep venous reflux and SVI.<sup>19–21</sup> Surgical treatments such as ulcer excision by 'shave therapy' and mesh grafting may also favour ulcer healing.<sup>22</sup> A limitation of the surgical approach is that some elderly and frail patients may be medically unfit for treatment or unwilling to undergo invasive management of their venous disease.

Systemic medications have been used in addition to standard treatments because of a theoretical ability to address one or more of the factors that have been identified in the pathophysiology of venous ulceration. A small number of drugs have been used with varying success. Stanazolol, a fibrinolytic anabolic steroid was expected to break down pericapillary fibrin cuffs<sup>23</sup> but did not increase the rate of ulcer healing.<sup>2</sup> Abnormalities of coagulation observed in patients with venous disease, have been improved by the use of aspirin.<sup>24</sup> In contrast, a thromboxane receptor antagonist (ifetroban) failed to show benefit over compression therapy in ulcer healing.<sup>2</sup>

Among phlebotropic drugs, the use of horse chestnut seed extract<sup>25</sup> and of hydroxyrutosides<sup>2</sup> resulted in a reduction in both oedema and symptoms of chronic venous insufficiency, but failed to demonstrate superiority over compression in advanced chronic venous insufficiency<sup>26</sup> or in preventing venous ulcer recurrence.<sup>27</sup> These findings may be because reduction in oedema alone is insufficient to treat leg ulceration. The involvement of growth factors<sup>28</sup> and leucocytes<sup>6</sup> in the development of venous ulceration has opened up new areas of investigation.

In a review of eight clinical trials, pentoxifylline improved venous ulcer healing on its own and when used in combination with compression compared with placebo.<sup>29</sup> Pentoxifylline is thought to work by reducing leucocyte adhesion to the vascular endothelium and through its anti-thrombotic effects. The way in which MPFF speeds ulcer healing might be by modulating leucocyte-L-selectin interaction with endothelial selectins responsible for the initial stages

of adhesion. By reducing the likelihood of leucocyte adhesion, MPFF presumably acts through an anti-inflammatory mechanism.<sup>6</sup> Thus, among the many mechanisms at work in the pathogenesis of venous ulceration, the mechanism involving leucocyte activation and interaction with the endothelium seems to be the one most responsive to pharmacological treatment up to now. The Kaplan–Meier curve (Fig. 2) shows that a trend in favour of MPFF began to emerge by week 8. This is comparable with the findings by Dale *et al.*<sup>30</sup> in which differences in healing rates between pentoxifylline and placebo were clear after the first 8 weeks of treatment. Eight weeks might be the period of time sufficient to influence the underlying microcirculatory abnormalities.

The rate of complete ulcer healing in the entire patient group included in our meta-analysis after 6 months is 55%. Previous studies in which compression alone has been used report complete healing rates of between 30 and 83% after 24 weeks of treatment.<sup>3,4,31,32</sup> The best healing rates come from trials performed in leg ulcer clinics with nurse specialists working under medical supervision<sup>4,31,32</sup> and the lowest rates from studies performed outside ulcer-oriented clinics.<sup>3,32</sup> Patients included in this meta-analysis were from a number of countries in which ulcers were treated in outpatient settings of specialized departments with a specific approaches to ulcer care. Healing rates in this analysis are within the range of those published from other centres. Compression applied in trials of this analysis was 30 mmHg at the ankle, judged by investigators to be the pressure most suitable for patient compliance and daily convenience. This most probably reflects the way in which compression is applied in daily practice.

In prognostic models,<sup>9</sup> ulcers exceeding 5 cm<sup>2</sup> and those persisting for more than 6 months are slower to heal with conventional therapy. Information regarding ulcer size is not always reported in published clinical trials on leg ulcer healing, making direct comparison difficult. The mean wound size in our meta-analysis (10.4 cm<sup>2</sup>) falls within the range where ulcers might be slow to heal.<sup>9</sup> Ulcer duration has been reported in the range 1–9 months in recent publications.<sup>3,4,32</sup> The study group in our meta-analysis had mean ulcer duration of 19.6 months that also might adversely affect the rate of healing. The entry criteria for studies included in the meta-analysis required ulcers which had been present for longer than 3 months in order to avoid wounds of traumatic origin that usually heal rapidly. The duration of venous disease is probably a further important factor determining ulcer healing, though its assessment depends upon patients' memory of events. The duration of ulcer disease (average

13.5 years) was recorded in 98% of our sample. This information is missing from many published clinical trials on leg ulcer healing.

Our results suggest that MPFF gives additional benefit to conventional therapy in ulcers between 5 and 10 cm<sup>2</sup> and those present for 6 to 12 months. No additional MPFF effect was shown in ulcers limited in size (<5 cm<sup>2</sup>) nor duration <6 months. This may be because compression treatment alone is all that is required in treating small ulcers of short duration. MPFF seems to be most appropriate when the venous ulcer disease has been present for less than 5 years.

None of the studies included in this analysis addressed the recurrence rate following healing. This is clearly an important point since recurrence of ulcers following healing is a common problem and contributes greatly to the cost of management of patients with leg ulcers. A prospective long-term study using adjunctive MPFF in patients with healed leg ulcers would be needed to answer this question. No such study has so far been performed.

In conclusion, we have found that oral treatment with MPFF in addition to standard compression treatment and wound management accelerates venous leg ulcer healing. No benefit was found in smaller ulcers of short duration (<6 months) that would in any case be expected to heal easily. Larger ulcers (5–10 cm<sup>2</sup>) of 6–12 months duration were found to benefit most from MPFF treatment. These ulcers tend to heal more slowly and an adjunctive treatment may be of advantage in such circumstances.

#### Acknowledgements

We thank Emmanuel Quinaux from IDDI (International Drug Development Institute, Belgium) for technical help in the data analysis, and Monika Lecomte from IRIS (Institut de Recherche International Servier, France) for providing the manufacturer's database. *Funding source.* We thank Les Laboratoires Servier (Neuilly-sur-Seine, France) for their financial support. *Conflict of interests.* Dr Coleridge Smith has received consulting and lecture fees from Credenthal, Med, Provensis, Servier and STD Pharmaceuticals. Dr Lok has received honoraria from Astra, Genevrier, Innothera, Phenix, Servier. Dr Ramelet has received consulting and lecture fees from Galderma, Innothera, Novartis, Masson, OM, Roche, and Servier.

#### References

- NELZEN O, BERGQUIST D, LINDHAGEN A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. *Br J Surg* 1994;**81**:182–187.
- ENNIS WJ, MENESES P. Standard, appropriate, and advanced care and medical-legal considerations: part two—venous ulcerations. *Wounds* 2003;**15**:107–122.
- Scottish Leg Ulcer Trial Participants. Effect of a national community intervention programme on healing rates of chronic leg ulcer: randomised controlled trial. *Phlebology* 2002;**17**:47–53.
- McMULLIN GM. Improving the treatment of leg ulcers. *Med J Aust* 2001;**175**:375–378.
- LYSENG-WILLIAMSON KA, PERRY CM. Micronised purified flavonoid fraction. A review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003;**63**:71–100.
- SHOAB SS, PORTER J, SCURR JH, COLERIDGE SMITH PD. Endothelial activation response to oral micronised flavonoid therapy in patients with chronic venous disease—a prospective study. *Eur J Vasc Endovasc Surg* 1999;**17**:313–318.
- NICOLAIDES AN. Investigation of chronic venous insufficiency: a consensus statement. *Circulation* 2000;**102**:e126–e163.
- VANSCHIEDT W, HEIDRICH H, JUNGER M, RABE E. Guidelines for testing drugs for chronic venous insufficiency. *Vasa* 2000;**29**:274–278.
- MARGOLIS DJ, BERLIN JA, STROM BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000;**109**:15–19.
- WHITEHEAD A, WHITEHEAD J. A general parametric approach to the meta-analysis of randomised clinical trials. *Stat Med* 1991;**10**:1665–1677.
- CUCHERAT M. *Meta-analyse des essais thérapeutiques*. Paris, Masson, 1997.
- GUILHOU JJ, DEREURE O, MARZIN L, OUVRY P, ZUCCARELLI F, DEBURE C *et al*. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomised, controlled *versus* placebo trial in 107 patients. *Angiology* 1997;**48**:77–85.
- GLIŃSKI W, CHODYNICKA B, ROSZKIEWICZ J, BOGDANOWSKI T, LECEWICZ-TORUN B, KASZUBA A *et al*. The beneficial augmentative effect of micronised purified flavonoid fraction (MPFF) on the healing of leg ulcers: an open, multicentre, controlled, randomised study. *Phlebology* 1999;**14**:151–157.
- ROZTOCIL K, STVRTINOVA V, STREJCEK J. Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. *Int Angiol* 2003;**22**:24–31.
- RIEGER H, ZUCCARELLI F. Clinical report (Lab Servier, France) on the effect of Daflon<sup>®</sup> 500 mg (2 tablets daily) on venous leg ulcers healing in 160 patients treated over a 6-month period. A multi-centre, double-blind, randomised, controlled *versus* placebo, parallel group study. Unpublished.
- MING KENG T. Analysis report (Lab Servier, France) on the efficacy and acceptability of oral Daflon 500 mg in the healing of venous leg ulcers in Singaporean population of 134 patients. A 4 month, double-blinded, placebo-controlled study: report prepared by Chan Siew Pang. Unpublished.
- ULLOA J. Double-blind, randomised, controlled *versus* placebo trial of Daflon 500 mg in venous leg ulcers in Latin America. Report (Lab Servier, France) prepared by Dr B. Detournay, S. Cros, A. Duburcq. Unpublished.
- SAVELIEV VS, POKROVSKY AV, KIRIENKO AI, BOGACHEV VY, BOGDANETZ LI, SAPEL'KIN SV *et al*. Analysis report (Lab Servier, France) of a randomised, multicentre comparative study of efficiency and safety of Detralex<sup>®</sup> in complementary treatment of complications of chronic venous insufficiency of lower extremities (trophic ulcers). Unpublished.
- BARWELL JR, DAVIES CE, DEACON J, HARVEY K, MINOR J, SASSANO A *et al*. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet* 2004;**363**:1854–1859.
- GOHEL MS, BARWELL JR, EARNSHAW JJ, HEATHER BP, MITCHELL DC, WHYMAN MR *et al*. Randomized clinical trial of compression plus surgery *versus* compression alone in chronic venous ulceration (ESCHAR study)—haemodynamic and anatomical changes. *Br J Surg* 2005;**92**:291–297.

- 21 GOHEL MS, BARWELL JR, WAKELY C, MINOR J, HARVEY K, EARNSHAW JJ *et al.* The influence of superficial venous surgery and compression on incompetent calf perforators in chronic venous leg ulceration. *Eur J Vasc Endovasc Surg* 2005;**29**:78–82.
- 22 SCHMELLER W, GABER Y. Surgical removal of ulcer and lipodermatosclerosis followed by split-skin grafting (Shave therapy) yields good long-term results in 'non-healing' venous leg ulcers. *Acta Derm Venereol* 2000;**80**:1–5.
- 23 BROWSE NL, BURNAND KG. The cause of venous ulceration. *Lancet* 1982;**2**:243–245.
- 24 LAYTON AM, IBBOTSON SH, DAVIES JA, GOODFIELD MJ. Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet* 1994;**344**:164–165.
- 25 DIEHM C, TRAMPISCH HJ, LANGE S, SCHMIDT C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet* 1996;**347**:292–294.
- 26 OTTILLINGER B, GREESKE K. Rational therapy of chronic venous insufficiency—chances and limits of the therapeutic use of horse-chestnut seeds extract. *BMC Cardiovasc Disord* 2001;**1**:5.
- 27 WRIGHT DDI, FRANKS PJ, BLAIR SD, BACKHOUSE CM, MOFFATT C, MCCOLLUM CN. Oxerutins in the prevention of recurrence in chronic venous ulceration: randomised controlled trial. *Br J Surg* 1991;**78**:1269–1270.
- 28 FALANGA V, EAGLSTEIN WH. The 'trap' hypothesis of venous ulceration. *Lancet* 1993;**341**:1006–1008.
- 29 JULI A, WATERS J, ARROLL B. Pentoxifylline for treatment of venous leg ulcers: a systematic review. *Lancet* 2002;**359**:1550–1554.
- 30 DALE JJ, RUCKLEY CV, HARPER DR, GIBSON B, NELSON EA, PRESCOTT RJ. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. *BMJ* 1999;**319**:875–878.
- 31 MOFFAT CJ, FRANKS PJ, OLDROYD M, BOSANQUET N, BROWN P, GREENHALGH RM *et al.* Community clinics for leg ulcers and impact on healing. *BMJ* 1992;**305**:1389–1392.
- 32 GHAURI ASK, NYAMEKYE I, GRABS AJ, FARNDON JR, WHYMAN MR, POSKITT KR. Influence of a specialized leg ulcer service and venous surgery on the outcome of venous leg ulcers. *Eur J Vasc Endovasc Surg* 1998;**16**:238–244.

Accepted 12 April 2005

Available online 3 June 2005