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Two Randomised and Placebo-controlled Studies of an Oral Prostacyclin Analogue (Iloprost) in Severe Leg Ischaemia

The Oral Iloprost in Severe Leg Ischaemia Study Group*

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Two separate studies are described using the same prostacyclin analogue in a similar group of patients.
Objectives: *to assess the tolerability and efficacy of two dose regimens of oral Iloprost compared with placebo in the treatment of patients with ischaemic ulcers, gangrene or rest pain due to severe arterial disease over a period of 4 weeks (Study A) and one year (Study B).*
Design: *multicentre, placebo controlled, double-blind, randomized prospective studies.*
Subjects & Methods: *178 (study A) and 624 (study B) patients with trophic skin lesions (ulcers or gangrene) or ischaemic rest pain due to severe arterial disease. To confirm severe arterial disease patients were required to have a systolic ankle Doppler pressure of 70 mmHg or less or a toe systolic Doppler pressure of 50 mmHg or less in one leg.*

In both studies patients were randomly allocated to three treatment groups: placebo, low dose Iloprost (50–100 μg twice a day) or high dose (150–200 μg twice a day)

In Study A the main outcome measures were tolerability of different doses of Iloprost and death, major amputation, healing of trophic lesions and relief of rest pain at the end of the follow up, which was 5 months after the end of the treatment. In Study B the primary end point was time to major amputation and stroke or death up to 12 months. Secondary pre-defined end points included the combined end point of patients alive without amputation, no trophic skin changes, no rest pain and not on regular analgesics.
Results: *the proportion of patients who completed the 4-week treatment period in Study A at the intended dose was 58%, 43%, 45% respectively in the placebo, low dose and high dose Iloprost groups. In an intention to treat analysis the proportion of patients who survived without major amputation, ulcers or gangrene and had no rest pain was 11% in the placebo group, 19% in the low dose iloprost group and 28% in the high dose Iloprost group. The pooled Iloprost groups showed a statistically significantly better result than the placebo group* ($p = 0.04$), *as did the high dose Iloprost group compared to the placebo* ($p = 0.014$).

In Study B there was no treatment benefit in terms of a primary end point of amputation and death. However the secondary combined end point of patients who survived without a major amputation, ulcers or gangrene and had no rest pain, nor a need for regular analgesia was favourable for Iloprost, with 18% of patients in the placebo group reaching this optimal secondary end point, compared to 23% in the low dose Iloprost group and 26% in the higher dose Iloprost group ($p < 0.05$).
Conclusions: *oral Iloprost administered for a year showed no clear benefit in patients with advanced severe leg ischaemia (PAOD III and IV). The results obtained with 4 weeks' treatment in Study A and in previous trials of intravenous Iloprost could not be reproduced*

Key Words: Iloprost; Prostacyclin; Critical leg ischaemia.

Introduction

Patients with ulcers, gangrene or rest pain due to severe arterial disease have a poor prognosis, both in terms of the need for major amputation and mortality. Twelve to thirty-two per cent of unselected newly diagnosed patients will be dead within the year and 10% to 20% of the survivors will have required a major amputation. Patients who have had an attempt at revascularisation, which has failed, have an even worse prognosis, with only about half of the patients being alive with two viable legs after 1 year.[1] Although the underlying pathology in these patients is major arterial occlusion, the final pathological results, that is skin breakdown or pain, are due to the microcirculatory response to a low perfusion pressure. This could theoretically be influenced by pharmacotherapy, for instance prostacyclin and its analogues. These drugs have been widely tested in this indication, initially administered intra-arterially and more recently intra-

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venously. To our knowledge the present study is the first to report the results of the effect of an orally active prostacyclin analogue in this indication.

Six double-blind placebo-controlled prospective trials of Iloprost, given intravenously, have been published so far.[2–7] Iloprost was given as a daily 6-hourly infusion in all the trials, with the period of treatment varying from 2–4 weeks. In two trials there was a formal 6 months' follow-up period. In all these intravenous studies the incidence of death or major amputation during the follow-up period was less in the Iloprost group than in the group receiving placebo and in two of the studies with 6 months' formal follow-up the difference was statistically significant. The principal disadvantage of the Iloprost treatment was that it had to be administered in hospital. An orally active compound would be more practical as these patients would not need to be hospitalised and treatment could be continued longer.

Study A was designed primarily to assess the tolerablity of two oral dosage regimens over a treatment period of 4 weeks. Encouraged by the apparent efficacy in this pilot study, Study B was carried out with treatment and observation over a year. Because 43% and 45% of the patients receiving Iloprost in Study A could not complete 4 weeks' treatment at the intended dosage, the two doses used in Study A were reduced in Study B from 100 μg to 50 μg twice a day in the low dose group, and from 200 μg to 150 μg twice a day in the higher dose group.

Patients and Methods

Study A was conducted in 35 centres in seven countries in Europe (France, Germany, Italy, Norway, Poland, Sweden and Great Britain). Study B was carried out in 37 centres in 10 countries (Finland, France, Germany, Great Britain, Hungary, Italy, Norway, Poland, Portugal and Sweden).

Patients with trophic skin changes (ulcers or gangrene) or rest pain due to severe arterial disease were entered; the inclusion criteria in the protocol were identical in the two studies. Rest pain requiring regular analgesia had to be present for 2 weeks. Underlying atherosclerosis was established by requiring the patients to have a maximum ankle systolic Doppler pressure of 70 mmHg or less, or a toe systolic pressure of 50 mmHg or less. The principal exclusion criteria were similar in the two studies: acute onset or rapid deterioration of the ischaemia, any revascularisation procedure in the previous 2 weeks, rapidly spreading cellulitis, regular treatment with an antiplatelet drug other than Aspirin or patients where revascularisation or major amputation was planned within the next two weeks.

Study A was a preliminary pilot study and therefore the primary end points were tolerability and safety of four week oral Iloprost treatment. Efficacy end points such as major amputation or death at the end of follow up period, total relief of rest pain without the need for analgesics and complete healing of trophic lesions were secondary end points. In Study B the primary end point of the trial was a combination of time to any major amputation or death during the 12-month treatment period. Secondary end points were the components of the primary end point individually, deterioration of PAOD necessitating other therapy, complete lesion healing in patients with trophic changes at baseline and complete relief of rest pain without regular use of analgesics. There was also a combined end point defined of patients who were alive, without a major amputation, with no trophic lesions, no rest pain without regular analgesics. The studies were approved by the relevant national and local ethical committees.

All patients received standard treatment for coexisting disease, pain relief, antibiotics if indicated and topical therapy for trophic lesions. In both studies patients were randomised to three treatment groups: placebo, low dose Iloprost or high dose Iloprost. In Study A the low dose group received 100 μg twice a day and the high dose group 200 μg twice a day, while in Study B the low dose group received 50 μg twice a day and the high dose group 150 μg twice a day. The intended dosage of Iloprost was reached after a titration period of 5 or 6 days. They were then maintained for a total of 28 days in Study A and for 1 year in Study B. In Study A patients were followed for 6 months after the start of the study medication. The dose could be reduced in both studies at any time if the patient developed unacceptableside effects. In Study B the treatment could also be interrupted temporarily, for instance while undergoing surgery, and then restarted at a dose level previously tolerated.

Results

Tables 1a and b show the demographic and baseline characteristics of the three treatment groups in the two studies. One hundred and seventy-eight patients were entered in Study A and 624 patients in Study B. In both studies the entry characteristics of the three treatment groups were similar, except that in Study A the proportion of diabetics in the placebo group was

Demographic and baseline characteristics of the treatment groups

Table 1a. Study A

	Placebo	Iloprost 100 μg b.i.d.	Iloprost 200 μg b.i.d
All patients	($n=62$)	($n=58$)	($n=58$)
Male	37 (60%)	34 (59%)	42 (72%)
Age (mean) (male)	69	71	67
(female)	73	78	73
Diabetic	24 (39%)	18 (31%)	20 (34%)
Smoker	12 (19%)	16 (28%)	14 (24%)
Rest pain only (stage Ill)	13 (21%)	21 (36%)	19 (33%)
Previous vascular intervention	21 (34%)	19 (33%)	23 (40%)
Previous major amputation	8 (13%)	7 (12%)	2 (3%)
Mean ankle systolic pressure	57 mmHg	54 mmHg	63 mmHg
Ankle pressure less than 20 mmHg	13%	12%	7%

Table 1b. Study B

	Placebo	Low dose Iloprost 50 μg b.i.d.	High dose Iloprost 150 μg b.i.d.
All patients	($n=207$)	($n=210$)	($n=207$)
Male (mean) male	65	66	65
female	75	74	74
Diabetic	57 (28%)	64 (31%)	70 (34%)
Smoker	59 (29%)	61 (29%)	59 (29%)
Rest pain only (Stage III)	95 (46%)	96 (46%)	96 (46%)
Previous vascular intervention	89 (43%)	92 (44%)	80 (39%)
Previous major amputation	17 (8%)	17 (8%)	18 (9%)
Mean ankle systolic pressure	57 mmHg	54 mmHg	58 mmHg
Ankle pressure less than 20 mmHg	8%	15%	8%

less than in the two Iloprost groups. Comparing the patients entered as a whole into the two studies, patients in Study B were approximately 5 years younger than in Study A and there were significantly more patients with rest pain alone (Stage III). The fact that these patients were not comparable to the group of newly diagnosed patients with PAOD III/IV is evidenced by the fact that approximately 35% of patients in Study A and 42% of patients in Study B already had a previous vascular intervention. The remaining patients were either deemed to be unsuitable for revascularisation or were entered into the study because revascularisation was thought to carry a high risk of failure.

In Study A complete discontinuation of treatment was actually higher in the placebo group (27%) than in the two Iloprost groups (22%). In Study A dose reductions were required in both Iloprost groups. In the high dose group, intended to receive 200 μg per dose, 78% tolerated 100 μg or more. However, in the low dose group, who were intended to receive 100 μg per dose, only 43% of the patients could tolerate this. It was for this reason that both the high and low dose doses of Iloprost were reduced in Study B. In Study B, where treatment was continued for a year, it had to be discontinued for adverse events in 39 patients on placebo, 44 on low dose Iloprost and 47 on high dose Iloprost. During the treatment and follow-up period of 6 months in Study A and one year in Study B only one and three patients, respectively, were lost to follow up in terms of primary end points.

Tables 2a and b summarise the efficacy result at the end of follow-up in the two studies, using an intention-to-treat analysis. In Study A 48% of the placebo patients were dead or had a major amputation by 6 months, while in Study B the comparable figure was 36% at 12 months. The efficacy data is also surprisingly different. In Study A the incidence of major amputation or death, complete pain relief and complete healing of trophic changes were all in favour both Iloprost groups compared to the placebo. The global efficacy assessment in terms of number of patients who were alive, without a major amputation, with no trophic changes and no rest pain at the end of the follow up period were 11% in the placebo group compared to 19% in the low dose and 28% in the high dose Iloprost groups. The difference between the pooled Iloprost groups and the placebo group was statistically significant ($p=0.04$) as well as the difference between the high dose Iloprost and the placebo groups ($p=0.01$). It was this favourable result in Study A, which was not powered to look at efficacy, which encouraged the

Table 2a. Efficacy results at 6 months in Study A.

	Placebo	Iloprost 100 μg b.i.d.	Iloprost 200 μg b.i.d.
All patients	($n=62$)	($n=58$)	($n=58$)
Major amputation	20 (32%)	14 (24%)	15 (26%)
Death	12 (19%)	8 (14%)	6 (10%)
Major amputation or death	30 (48%)	20 (34%)	19 (33%)
Alive, without major amputation, no ulcer or gangrene and no rest pain*	7 (11%)	11 (19%)	16 (28%)
Stage III	($n=13$)	($n=21$)	($n=19$)
Complete pain relief*	4 (31%)	7 (33%)	9 (47%)
Stage IV	($n=49$)	($n=37$)	($n=39$)
Complete healing of ulcers and gangrene	6 (12%)	7 (19%)	10 (26%)

Table 2b. Efficacy results at the end of 12 months' treatment in Study B.

Event	Placebo	Low dose Iloprost 50 μg b.i.d.	High dose Iloprost 150 μg b.i.d.
All patients	($n=207$)	($n=210$)	($n=207$)
Major amputation	61 (30%)	55 (26%)	52 (25%)
Death	25 (12%)	23 (11%)	32 (16%)
Major amputation or death	74 (36%)	71 (34%)	72 (35%)
Alive, without major amputation, no skin lesions, no pain*	37 (18%)	49 (23%)	54 (26%)
Stage III	($n=95$)	($n=95$)	($n=96$)
Complete relief of rest pain*	23 (24%)	26 (27%)	34 (39%)
Stage IV patients	($n=112$)	($n=114$)	($n=111$)
Complete healing of ulcers and gangrene	22 (20%)	34 (30%)	27 (24%)

* Counting patients with no rest pain and no regular analgesics use, alive without major amputation.

investigators to proceed to a larger Study B with a 1-year treatment and observation period. Unfortunately the beneficial trends seen in Study A were not reproduced. There was no difference between the three groups in the primary end point of major amputation and/or death. Explorative univariate subgroup analyses of patients with Stage III or Stage IV, diabetic or non diabetic, ankle systolic pressure above or below 20 mmHg at entry did not reveal a clear difference from the overall result in any of the subgroups when analysed for the primary end point. In the pre-specified combined secondary end point of patients alive, without a major amputation, with no trophic lesions, no rest pain and no regular use of analgesics. The difference between the three groups was significant ($p<0.05$). 18% of patients in the placebo group reached this optimal secondary end point, compared to 23% in the low dose Iloprost group and 26% in the higher dose Iloprost group.

Discussion

Discontinuation due to side effects did not differ significantly between the Iloprost and placebo groups, but the results suggest that titrating the dose over the first few days results in better compliance with the higher doses. Both studies also suggest that incidence of side effects declined rapidly over the first few weeks. The relatively high healing rates in both studies in patients with trophic changes, both in the Iloprost and in the placebo groups, was probably due to all patients receiving standard care, including treatment of pre-existing cardiac disease and the local treatment to trophic lesions.

Six double-blind placebo controlled studies[2–7] of Iloprost given intravenously for up to 4 weeks have been published so far in a total of 740 patients with severe leg ischaemia causing trophic changes or rest pain. Two hundred and seventy patients participated in two trials where there was a prospective follow-up of 6 months. Both trials showed statistically significant reduction in major amputation or death at 6 months in favour of the Iloprost groups. The pooled ITT results from these two trials, including additional retrospectively collected follow-up information from the other trials, showed the incidence of major amputation and/or death in the placebo group was 57% compared to 40% in the Iloprost groups. It therefore seemed reasonable to proceed to a similar study when an oral

formulation of Iloprost became available. As far as we are aware, these are the first reports of studies an oral formulation of a prostacyclin analogue in a prospective double-blind placebo-controlled study in patients with severe leg ischaemia. In the smaller Study A on an intention to treat analysis, the incidence of major amputation and/or death in the placebo group was 48%, slightly less than in the previous intravenous studies. However the advantage in favour of Iloprost was very similar in the 4-week intravenous trials and the 4-week oral Study A. The results of the larger Study B, where oral Iloprost was given for a year, could not however reproduce similar differences in amputation and/or death rate between placebo and the treated groups. Both studies, however, were statistically significant in favour of Iloprost in terms of one predefined secondary end point, that is patients alive without an amputation, no trophic changes, no rest pain and not requiring regular analgesia. This end point could be said to represent the optimal short to medium term outcome for these patients. However, as the primary end point in the larger Study B failed to show a statistically significant effect, the overall results should be interpreted with great caution.

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Addendum

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