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Topical Calcipotriol plus Oral Fumaric Acid Is More Effective and Faster Acting than Oral Fumaric Acid Monotherapy in the Treatment of Severe Chronic Plaque Psoriasis vulgaris

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Key Words
Psoriasis vulgaris · Calcipotriol · Fumaric acid esters (FAEs) · Clinical trial · Pharmacoeconomics

Abstract
Background: Calcipotriol is an established topical therapy for psoriasis vulgaris. ***Objective:*** This study aimed to investigate whether the addition of calcipotriol to fumaric acid ester (FAE) monotherapy had an additive efficacy and an FAE-sparing effect in patients with severe plaque psoriasis. ***Methods:*** This multicentre, randomised, double-blind, vehicle-controlled study included 143 patients for up to 13 weeks treatment. Group A received FAE tablets (Fumaderm®) with an increasing daily dosage from 105 to 1,075 mg + ointment vehicle. Group B received FAE tablets + calcipotriol ointment (50 μg/g). Ointments were applied twice daily. Clinical response was assessed using percentage changes in the Psoriasis Area and Severity Index (PASI), from baseline to treatment end. ***Results:*** The mean percentage change in the PASI was –76.1% in group B and –51.9% in group A, the difference between treatments was –24.2% (95% CI from –34.2 to –14.2%; $p < 0.001$). Group B responded more rapidly to treatment. Investigators' and patients' overall efficacy assessments were significantly more favourable for group B ($p \leq 0.001$). Group B was prescribed less FAE than group A. This difference was greatest at the last visit (mean daily dose 529 and 685 mg, respectively; $p = 0.006$). Overall adverse events in the two groups were similar. ***Conclusion:*** This study shows that the combination of calcipotriol and FAEs is significantly more effective and faster acting than FAE monotherapy in the treatment of severe plaque psoriasis. The combination has a slight FEA-sparing effect and therefore a superior benefit/risk ratio.

Introduction

Psoriasis is a very common chronic relapsing skin disease with a prevalence in central Europe of about 2–3% [1, 2]. Today, its aetiology can be much better explained,

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but as a polygenic disease with an autoimmune pathomechanism involving both the epidermal/dermal compartments and the T-cell-immune system koebnerized by internal and external factors it is far away from being fully understood [1–7]. The therapeutic armamentarium mostly comprises topical and systemic drugs or methods affecting both or alone the processes of epidermal hyperproliferation and differentiation, and the epidermal tropism of T cells and polymorphonuclear granulocytes.

Vitamin D_3 derivatives and fumaric esters are both involved in inhibiting these pathways. Calcipotriol has been demonstrated to be equivalent to or more effective than dithranol [8], coal tar [9] and at least as effective as steroids [10, 11]. It is effective in the long term [12] and has been successfully used in combination with systemic treatments [13, 14] and, as well as other vitamin D_3 derivatives, with phototherapy [15–17]. Calcipotriol is well tolerated, even in children [18], with no effect on hepatic or renal function or calcium haemostasis [19]. Calcipotriol and other vitamin D_3 derivatives act via the $1,25(OH)_2$ D_3 receptor of keratinocytes and lymphocytes in differentiation and proliferation with little effects on calcium metabolism [20] and are well established, effective and safe treatment options.

Systemic treatment with fumaric acid esters (FAEs) has also been shown to be effective in clinical studies, eliciting an improvement in up to 75% of patients [21–23]. Its mode of action most probably leads to a switch of Th1 to Th2 T cell activity (IL-10↑) on the one hand [24–27], and, on the other hand, to keratinocyte proliferation [28]. Studies have shown superior improvement when a combination of FAEs was used, but several reversible side-effects were seen in these studies, including eosinophilia and leukopenia [22, 23, 29]. Up to 25% of patients treated with FAEs withdrew from studies due to adverse events. There have been reports on nephro- and hepatotoxicity [30–32] which, however, could not be confirmed in controlled studies with larger patient collectives [22, 23]. FAEs are considered to be an effective long-term treatment for severe psoriasis, but it is recommended that patients be regularly monitored [33, 34]. The threat of side-effects can influence compliance in patients taking FAEs, so monotherapy with FAEs is not necessarily adopted.

The aim of this study was to determine whether the addition of calcipotriol to the treatment with FAEs may have an additive therapeutic and an FAE-sparing effect in patients with severe chonic plaque psoriasis and to assess the efficacy, safety and tolerability of this therapeutic combination.

Patients and Methods

Study Design

The study was a prospective, multicentre, randomised, double-blind, vehicle-controlled, parallel-group, comparative study on the efficacy and safety of the combination of FAEs and calcipotriol. Patients received FAEs + placebo (calcipotriol ointment vehicle) or FAEs + calcipotriol ointment (50 μg/g). The study was divided into two phases: the initial wash-out and qualification phase with emollient cream took place over a 2-week period and was followed by a double-blind treatment phase of 13 weeks' duration.

Study Population

A total of 143 patients with severe psoriasis vulgaris were recruited into the study. Recruits were hospital in-patients and out-patients, aged ≥ 18 years and with a clinical diagnosis of severe psoriasis vulgaris for whom treatment with FAEs was deemed appropriate. Standard exclusion criteria applied.

Study Medication

Treatment with either calcipotriol ointment (50 μg/g) or placebo (vehicle ointment) was randomly assigned to each patient. The ointments were similar in appearance, smell and texture. They were applied twice daily without occlusion to affected skin areas, up to a maximum of 120 g per patient per week. FAEs (Fumaderm®, Fumedica GmbH) were provided in the form of tablets, and all patients started with a dose of 105 mg/day (1 tablet Fumaderm® P mite; week 0). The dose was increased weekly as far as possible, reaching 645 mg/day (3 tablets Fumaderm® P forte) by week 5, after which the dose was individualised for each patient at the physician's discretion. A maximum daily dose of 1,075 mg was not exceeded. An emollient cream (Abitima®, Dumex GmbH) was additionally provided during the wash-out/qualification period and double-blind treatment phases.

Clinical Assessments

Response was assessed using percentage changes in the Psoriasis Area and Severity Index (PASI), from baseline (at visit 2) to the end of treatment. The PASI was assessed at each visit. Investigator and patient also gave an assessment of overall response to treatment at each postrandomisation visit, grading the overall response on a 6-point scale of cleared, marked improvement, moderate improvement, slight improvement, unchanged or worse. Adverse events were recorded and clinical and laboratory parameters assessed.

Statistical Evaluation

Approximately normally distributed data on an interval scale are described by the mean, standard deviation, minimum and maximum values. For data on a nominal or ordinal scale, the number and percentage of patients in each category are presented. The results of all statistical analyses are presented as the estimate of treatment effect, 95% confidence interval (CI) and p values.

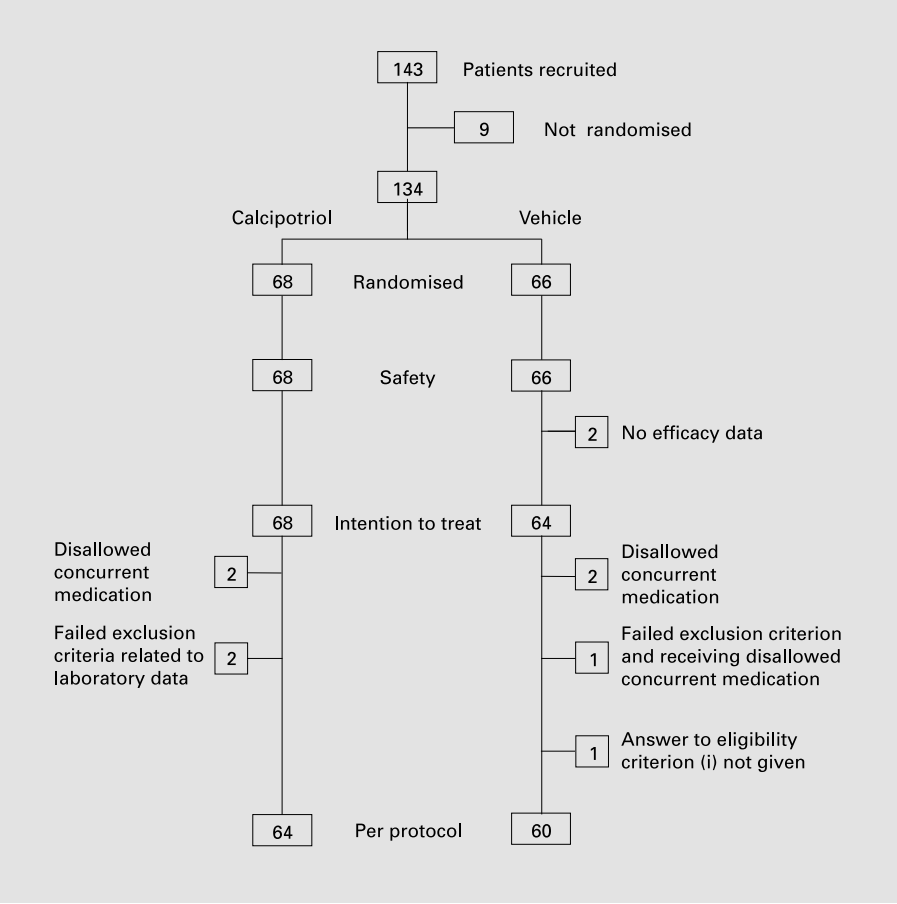

Fig. 1. Schematic presentation of patient populations.

Results

Patient Numbers and Demographics

In total, 143 patients were recruited into the study from 16 centres in Germany and 1 centre in the Netherlands. The patient population as included in the study is schematically represented in figure 1. During the course of the study, a total of 34 (25.4%) patients withdrew, 14 (20.6%) in the combination group and 20 (30.3%) in the FAE monotherapy group (table 1). The combination and monotherapy groups were well matched at baseline for age (43.4 vs. 43.6 years, respectively), the proportion of patients with a duration of psoriasis >10 years (69.1 and 68.2%, respectively) and distribution of skin type (73.5 and 72.7% of patients, respectively, had skin type II or III). There were slightly more males in the FAE monotherapy group (75.8 vs. 64.7% in the combination group). Changes in the PASI between visits 1 and 2 of the washout period and at baseline (visit 2) were similar between the two treatment groups (17.4 at baseline in the combination group and 17.7 in the FAE monotherapy group; intention-to-treat, ITT, population).

Change in PASI from Baseline to End of Treatment

In both treatment groups the PASI was lower at the end of treatment compared with baseline (fig. 2). The mean percentage change in the PASI adjusted for the effect of centre and baseline PASI was –76.1% in the combination group and –51.9% in the FAE monotherapy group (ITT population). The difference between treatments (calcipotriol – vehicle) was –24.2% (95% CI from –34.2 to –14.2%), which is statistically significant ($p < 0.001$).

Treatment Response

In the investigators' overall efficacy assessments at the end of treatment, the odds ratio for calcipotriol relative to vehicle was 3.06 (95% CI 1.57–5.95), indicating a statistically more favourable effect for the combination group compared with the FAE monotherapy group ($p < 0.001$;

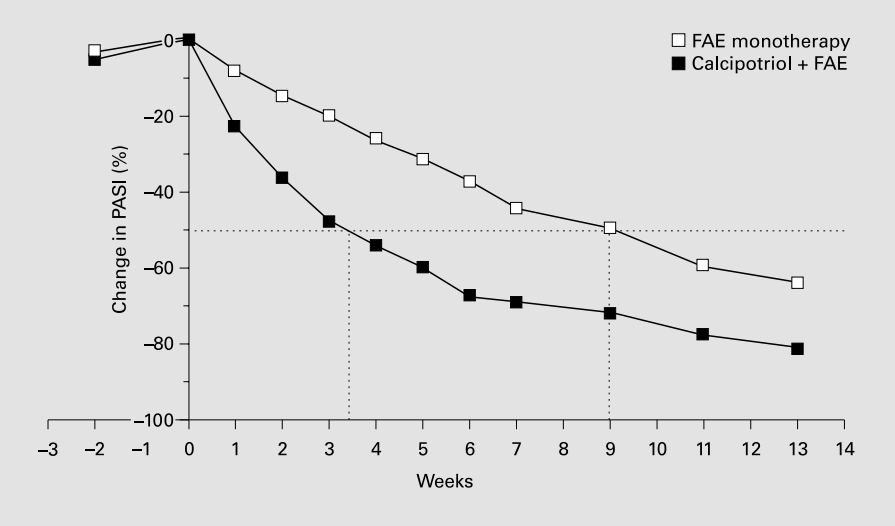

Fig. 2. Percentage change in PASI at each visit (ITT population).

Table 1. Reasons for withdrawal from the study

	Calcipotriol (n = 68)		Vehicle (n = 66)	
	n	%	n	%
Gastro-intestinal side-effects	4	5.9	4	6.1
Flush	1	1.5	0	0
Renal colics	0	0	1	1.5
Fatigue + loss of concentration	0	0	1	1.5
Headache + increased sweating	0	0	1	1.5
Itching	1	1.5	1	1.5
Local irritation/allergic reaction	2	2.9	0	0
Eosinophilia	2	2.9	2	3.0
Liver enzymes increased	2	2.9	1	1.5
Unacceptable treatment response	1	1.5	5	7.6
Renal clearance insufficient	0	0	1	1.5
Acute-phase MS	0	0	1	1.5
Lost to follow-up	0	0	2	3.0
Voluntary	1	1.5	0	0
Intensive sunbathing	0	0	1	1.5
Travel	1	1.5	0	0

For one patient in each treatment group, two reasons for withdrawal for each patient are listed. MS = Multiple sclerosis.

fig. 3). The results of the patients' assessments were similar to those of the investigators ($p = 0.001$). The investigators' assessments all showed a significantly greater reduction in extent score ($p = 0.008$), redness, thickness and scaliness scores (all $p < 0.001$) for the combination group compared with the FAE monotherapy group.

Speed of Reaction to Treatment

The combination group responded more rapidly to treatment, with a 50% reduction in the PASI score evident after 3 weeks of treatment, compared with 9 weeks for the FAE monotherapy group.

Dosing

The combination group was prescribed 4.5 g less FAE across the entire course of the study than the FAE monotherapy group (95% CI 11.6 g less to 2.5 g more, p = 0.2; fig. 4). The difference was significant at the last visit that FAEs were prescribed (mean 154 mg less; 95% CI from –262 to –45 mg; p = 0.006).

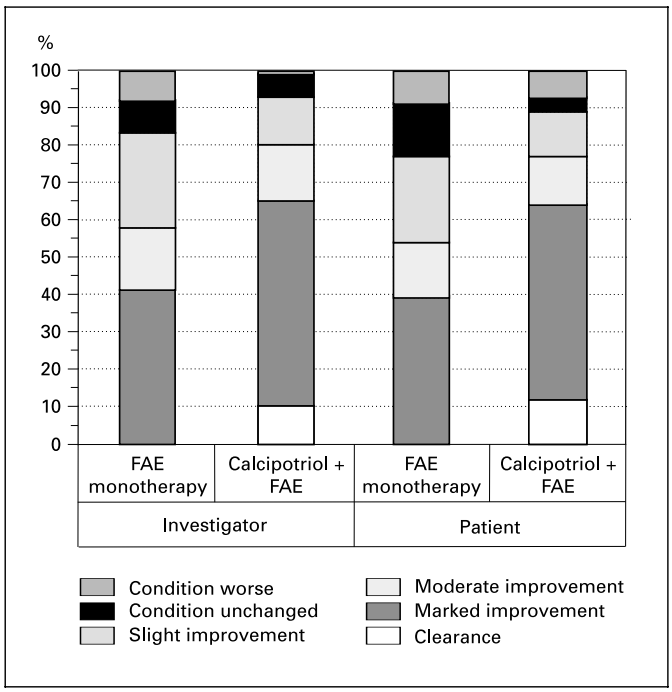

Fig. 3. Patients' and investigators' overall assessments at the last visit in the FAE monotherapy group and calcipotriol + FAEs group.

Safety Assessments

In this study, the numbers of patients reporting adverse events in the two groups were similar: 56 patients (82.4%) in the combination group versus 52 (78.8%) in the FAE monotherapy group. There was no statistically significant difference between the treatment groups with respect to the proportion of patients who reported adverse events (p = 0.60; odds ratio 1.26, 95% CI 0.53–2.96). The most commonly reported adverse events in the combination and FAE monotherapy groups were diarrhoea (22 and 24 patients, respectively), flushing (23 and 17), abdominal pain (16 and 14) and pruritus (10 and 14). With regard to the intensity of adverse reactions to calcipotriol, patients randomised to receive the combination treatment experienced 25 adverse reactions (16 mild, 5 moderate, 4 severe); patients randomised to receive FAE monotherapy experienced 16 adverse reactions (4 mild, 7 moderate, 5 severe). In the calcipotriol group, the severe adverse reactions were contact dermatitis (1 patient), pruritus (2 patients) and erythematous rash (1 patient). In the FAE monotherapy group, the severe adverse reactions rated possibly related to calcipotriol by the investigators were eosinophilia, headache, pruritus (2 patients) and increased sweating. Only 1 serious adverse event was reported ('adnexitis' diagnosed in a patient in the combination group), and this was considered unlikely to be related to the study medication and the patient continued the study. No patients were above the upper limit of the reference range for albumin-adjusted calcium at the end of treatment in either group. Clinical chemistry parameters did not alter significantly within patients during treatment with the study medication. Three patients (2 calcipotriol; 1 vehicle) were withdrawn from the study due to

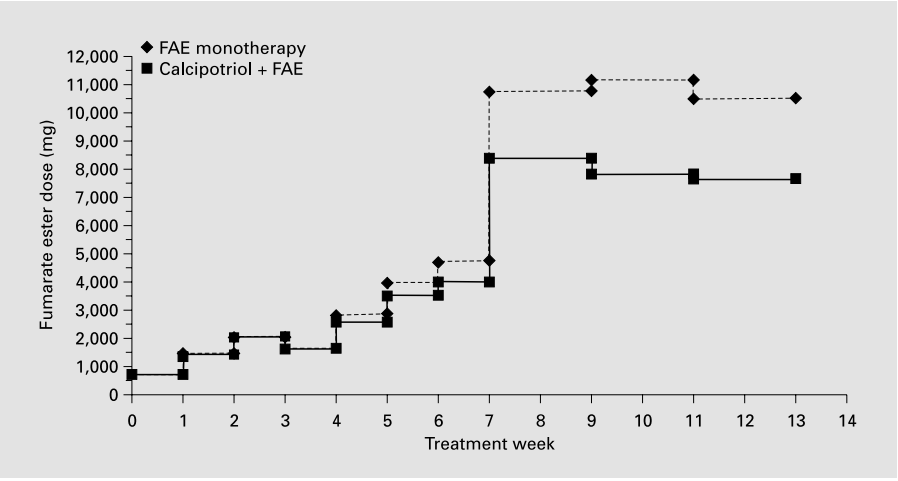

Fig. 4. Mean fumarate ester dose prescribed by treatment week.

increasing values for liver enzymes under FAE therapy. Four patients (2 calcipotriol; 2 vehicle) withdrew from the study due to eosinophilia emerging during FAE therapy. There were also some small but nonsignificant changes in leukocyte and lymphocyte counts. No other clinically important changes were seen for any clinical chemistry, haematology or urinalysis parameters. All patients leaving the study with clinically significant changes in clinical chemistry or haematology parameters were followed up until the respective parameter(s) had returned to normal.

Discussion

Treatment of the chronic plaque type of psoriasis is very much depending on the size of the involved body area and the severity (PASI score), i.e. whether topical therapy alone or a combination with an oral antipsoriatic drug has to be chosen to induce a long-term relapse-free interval. However, we have to consider that this is not always a realistic expectation [35]. The aim of this study was to determine whether the addition of calcipotriol to treatment with FAEs may have an additive therapeutic and an FAE-sparing effect in patients with severe chronic plaque psoriasis and to assess the efficacy, safety and tolerability of this therapeutic combination.

With both treatments we could document a significant decrease in the PASI score from baseline to the end of the treatment period; however, the addition of calcipotriol treatment to FAE monotherapy produced a statistically significantly better treatment response compared with FAE therapy alone.

No controlled studies have reported yet on the combination of FAEs with a topical treatment regimen. However, data from the present study can be compared with previous studies on fumaric acid monotherapy in severe psoriasis, if slight differences in study design and analysis are taken into consideration. Mrowietz et al. [23] reported a mean PASI reduction of 65% after an FAE treatment period of 13 weeks, which is identical to the 64.9% PASI reduction observed in the present study in patients who completed treatment with FAEs alone (when drop-outs are excluded from the analysis). Including drop-outs in the analysis, Altmeyer et al. [22] reported a PASI reduction of 50.1% after an FAE monotherapy of up to 16 weeks. Again this is similar to the 51.9% PASI reduction seen in the present study (including drop-outs) following 13-week FAE monotherapy. In the present study, the greater improvement of psoriasis in terms of greater percentage reduction in PASI seen in the combination therapy is confirmed by the investigators' and patients' overall assessments of treatment efficacy. Both assessments showed a significantly more favourable response for the combination group compared with the FAE monotherapy group. Other response criteria also supported this finding, and the most marked differences in response between the two groups were observed before week 4 of treatment. This latter finding supports observations by Altmeyer et al. [22] of a late response to FAE monotherapy.

The dose of FAEs required by patients during the study as a whole was 4.5 g lower in the combination group, suggesting that the combination did indeed produce an FAE-sparing effect. At the last visit, the combination group was prescribed significantly less FAE than the monotherapy group (mean daily dose 529 and 685 mg, respectively). These data suggest that therapy with FAEs can be extended to combination with calcipotriol, resulting in an FAE-sparing effect that is most pronounced at the last visit. Furthermore, the drug-sparing effect in FAEs with calcipotriol increases the safety/risk ratio during a 3-month treatment course.

In total, 34 patients (25.4%) withdrew prematurely from randomised treatment in the present study. However, in a similar open non-controlled study [23], a drop-out rate of 30% was reported. An even greater number of drop-outs were reported in a blinded, placebo-controlled study on psoriasis treatment with FAEs (38.8% of the treatment group and 58.0% of the placebo group) [22]. In that study, most drop-outs in the placebo group resulted from worsening of psoriasis and the FAE group from gastro-intestinal side-effects. In the present study, a similar 30.3% drop-out rate was observed for the FAE group, but a much lower rate of 20.6% was recorded for the calcipotriol combination group.

There were no statistically significant differences between the two treatment groups in adverse events reported by patients in our study. Within both treatment groups, the adverse reactions to FAEs corresponded closely in type and quantity with their known side-effects such as gastro-intestinal complaints and flushing. Combination therapy did not cause any reported change in kidney function, although FAEs are suspected of having a nephrotoxic effect at certain doses [30–32]. This tolerability was observed even when high doses of calcipotriol (up to 120 g/week) were used. No clinically important changes in calcium metabolism were reported in this study at the highest calcipotriol doses (which at 120 g/week were higher than the manufacturer's recommended dose of 100 g/week). In previous studies, FAEs have been associated with a range of adverse effects, including transient eosino-

philia, mild lymphocytopenia as well as gastro-intestinal complaints and flushing [22, 23]. In view of this, guidelines have been devised to improve the safety and efficacy of FAE treatment for psoriasis [34]. The guidelines recommend FAE use in combination with other treatment modalities though not phototherapy, as FAEs may be immunosuppressive agents. Calcipotriol is an obvious choice and the results of the present study suggest that, during treatment, the side-effects of both FAEs and calcipotriol remain unchanged when used in combination.

Calcipotriol has been previously shown to be well tolerated and efficacious in combination with numerous other psoriatic treatments, including topical therapies [13], phototherapy [15, 16] and systemic therapy [13, 14]. A study was carried out to investigate the addition of calcipotriol ointment (50 μg/g) to systemic retinoid acitretin therapy in psoriasis [14]. Its combination with calcipotriol ointment was found to produce an additional therapeutic effect and an acitretin-sparing effect.

In conclusion, the combination of FAEs with calcipotriol is significantly more effective and faster acting than FAE monotherapy in severe chronic plaque-like psoriasis. The combined use of calcipotriol and FAEs also results in an FAE-sparing effect and thus offers a superior benefit/risk ratio to FAE monotherapy. These data further support the benefits when using calcipotriol in combination with systemic antipsoriatic therapy.

List of Participating Centres

Bad Salzschlirf: W. Küster; Bochum: P. Altmeyer; Darmstadt: M. Hagedorn; Dresden: G. Wozel; Essen: M. Goos; Frankfurt: R. Kaufmann; Freiburg: E.J. Schöpf; Hamburg: I. Moll; Hannover: A. Kapp; Kassel: J. Petres; Kiel: E. Christophers; Köln: T. Krieg; Leiden: S. Pavel; Magdeburg: H. Gollnick; München: J. Ring: Münster: T. Luger; Oberhausen: N. Weindorf.

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