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n-3 Fatty acids in psoriasis

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Increased concentrations of free arachidonic acid (AA) and its proinflammatory metabolites have been observed in psoriatic lesions. Replacement of arachidonic acid by alternative precursor polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA), which can be metabolized via the same enzymatic pathways as AA, might be a therapeutic option in psoriasis. However the results of studies evaluating the therapeutic benefit of dietary fish oil have been conflicting and not clearly dose-dependent. To overcome the slow kinetics and limited availability of oral supplementation, we have performed three studies to assess the efficacy and safety of an intravenously administered fish oil derived lipid emulsion on different forms of psoriasis. Patients received daily infusions of either an *n*-3 fatty acid-based lipid emulsion (Omegaven®) or a conventional *n*-6 lipid emulsion (Lipoven®) in different time and dose regimens. In addition to an overall assessment of the clinical course of psoriasis, EPA- and AA-derived neutrophil 5-lipoxygenase (LO)—products, thromboxane (TX) B_2/B_3, PAF and plasma free fatty acids were investigated. Treatment with *n*-3 fatty acids resulted in a considerably higher response rate than infusion of *n*-6 lipids. A more than 10-fold increase in neutrophil EPA-derived 5-LO product formation was noted in the *n*-3 group, accompanied by a rapid increase in plasma-free EPA within the first days. In conclusion, intravenous *n*-3-fatty acid administration causes reduction of psoriasis, which may be related to changes in inflammatory eicosanoid generation. The rapidity of the response to intravenous *n*-3 lipids exceeds by orders of magnitude the hitherto reported kinetics of improvement of psoriatic lesions upon use of oral supplementation.

***n*-3 Fatty acids: Fish oil: Psoriasis: Inflammation: Eicosanoids**

Introduction

Psoriasis is a common inflammatory skin disorder, affecting 2% of the population in western countries. It is characterized by pronounced hyperproliferation of keratinocytes, combined with markedly increased vascularization of the skin, fibroblast activation and *leucocyte* infiltration (Christophers & Sterry, 1993). The pathogenesis has not been entirely clarified (Christophers, 1996). The role of infiltrating white blood cells in initiating psoriasis has stimulated a search for chemotactic and proinflammatory factors, of which cytokines and lipid mediators have emerged as principal protagonists. As part of a multifactorial process, profound changes in the metabolism of eicosanoids with increased concentrations of free arachidonic acid and its pro-inflammatory metabolites (leukotriene B_4—LTB_4, hydroxyeicosatetraenoic acids—HETE) have been observed in psoriatic lesions (Christophers & Sterry, 1993; Grimminger & Mayser, 1995). These metabolites have a chemotactic effect on skin-infiltrating *leucocytes*, in particular on neutrophils, and may enhance keratinocyte proliferation.

Release of free arachidonic acid from membrane phospholipid pools is the rate-limiting step in eicosanoid synthesis. LTB_4 generated by the neutrophil can stimulate the cell in an autocrine way (Mahadevappa & Powell, 1989; Grimminger *et al.* 1992). Interestingly, keratinocytes can cooperate in leukotriene synthesis. Intermediate LTA_4 secreted by the neutrophil can be further metabolized by adjacent keratinocytes (Sola *et al.* 1992; Iversen *et al.* 1993). The resulting chemotactic gradient may direct the activated neutrophil from the microvessel towards the subcorneal microabcesses in psoriatic skin lesions.

Therefore, replacement of arachidonic acid by alternative precursor polyunsaturated fatty acids (PUFA), especially eicosapentaenoic acid (EPA), might be a therapeutic

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFA, free fatty acids; HETE, hydroxyeicosatetraenoic acid; LTB_4, leukotriene B_4; LTB_5, leukotriene B_5; PASI, psoriasis area and severity index; PMN, polymorphonuclear leucocyte; PUFA, polyunsaturated fatty acid; T_h, T-helper cell; T_x, thromboxane.

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starting point in psoriasis. EPA, the *n*-3 pentaene analogue of AA, can be metabolized via the same enzymatic pathways as AA (Goldman *et al.* 1983; Lee *et al.* 1984; Heidel *et al.* 1989). However, the chemotactic and neutrophil-activating capacity of LTB_5 derived from EPA is more than ten times lower than that of LTB_4 and it is a less potent stimulator of keratinocyte proliferation (Kragballe *et al.* 1987).

A number of studies have evaluated the therapeutic benefit of *n*-3 fatty acids in psoriasis, either using fish oil or highly purified *n*-3 fatty acid ethyl esters. However, despite the fact that sometimes high amounts of *n*-3 fatty acids are ingested by the patients, the results have been conflicting and not clearly dose-dependent (Grimminger & Mayser, 1995; Table 1). Therefore, we conducted three studies addressing acute-exanthematic and chronic-plaque type manifestations of psoriasis with extended skin involvement in hospitalized patients with intravenous application of EPA (Grimminger *et al.* 1993*a*; Mayser *et al.* 1996, 1998). The intravenous route was chosen to guarantee rapid availability of *n*-3 fatty acids and to provide increased plasma levels of EPA in non-esterfied form. Free EPA can directly compete with AA at the level of intracellular eicosanoid synthesis and so can potentially exert a rapid and profound effect on inflammatory activity in psoriatic lesions (Grimminger *et al.* 1992).

Description of the studies

All trials were conducted with identical lipid emulsions (Omegaven or Lipoven) obtained from Fresenius AG, Oberursel, FRG. Their composition is shown in Table 2.

In the first double-blind, parallel-group, placebo-controlled study conducted in 1990–1, 20 patients with acute-exanthematic psoriasis were randomly allocated to receive twice daily infusions of 50 ml *n*-3 fatty acid-based lipid emulsion (Omegaven) or conventional *n*-6-lipid emulsion (Lipoven) for 10 days (Grimminger *et al.* 1993*a*). In addition to clinical parameters (erythema, infiltration, desquamation, subjective score) neutrophil 4- *v.* 5-series leukotriene generation was investigated. During the trial period additional psoriasis therapy was restricted to topical application of 0·03 % cignolin in white petrolatum.

In a second trial, a patient with relapsing acute-exanthematic psoriasis was twice under therapy with an *n*-3 lipid emulsion (Mayser *et al.* 1996). In the first 10-day intervention, he received 50 ml Omegaven twice daily. Additional anti-psoriatic therapy was restricted to topical application of 0·03 % cignolin vaseline. The severity of the disease was evaluated by the Psoriasis Area and Severity Index (PASI)-Score (Fredriksson & Petersson, 1978). One year later, the patient asked for a second intervention with Omegaven because of his previous good experience. Since the relapse was much more extended, the previous dose was doubled (2 × 100 ml) and therapy was performed for a period of 15 days. During the intervention, therapy was restricted to bland emulsifying ointment.

The third trial, a double-blind, randomized, parallel group study, was performed in eight European centers for dermatology (Mayser *et al.* 1998). Eighty-three patients hospitalized for chronic-plaque-type psoriasis with a severity of at least 15 according to PASI were randomly allocated to receive twice daily infusions with 100 ml Omegaven or Lipoven for 14 days. Efficacy of therapy was evaluated by changes in PASI, in an overall assessment of psoriasis by the investigator, and a self-assessment by the patient. In one center neutrophil 4- *v.* 5-series leukotriene (LT) generation and platelet 2- *v.* 3-thromboxane generation were investigated and plasma-free fatty acids were determined.

The details of these three trials are summarised in Table 3.

Results of the trials

In all trials *n*-3 lipid emulsion had a positive influence on the course of psoriasis. The effect seemed to be more pronounced in the inflammatory, acute-exanthematic forms of the disease. Obvious side-effects of the lipid

Table 1. Studies to evaluate the therapeutical benefit of orally applied *n*-3 fatty acids, either using fish oil or highly purified *n*-3 fatty-acid ethyl esters

Author/year	Design[a]	Route	Clinical form/cases completed	Days	Oil[b] (g/d)	EPA (g/d)	DHA (g/d)	Result[c]
Ziboh *et al.* 1986	open	oral	stable-plaque/13	56	60–75*	10·8–13·5	7·2–9·0	+
Maurice *et al.* 1987	open	oral	stable-plaque/10	42	25–50*	4·5–9·0	6·0	+
Bittiner *et al.* 1988	db. pc	oral	stable-plaque/28	56	10*	1·8	1·2	+
Bjorneboe *et al.* 1988	db. Pc	oral	stable-plaque/27	56	10*	1·8	1·2	−
Kettler *et al.* 1988	open	oral	stable-plaque/22 pustular/1	*ca.* 50	18*	3·2	2·2	−
Kragballe *et al.* 1989	open	oral	stable-plaque/26	120	30*	5·4	3·6	+
Kojima *et al.* 1989	open	oral	stable-plaque/9	90–180	4**	3·6		+
Schena *et al.* 1989	open	oral	stable-plaque/13	56	20***	1·3	1·7	+
Dewsbury *et al.* 1989	sb. pc	topical	stable-plaque/11	49	–*			+
Lassus *et al.* 1990	open	oral	stable-plaque/76 (34 with arthritis)	56	6**	1·1	0·8	+
Linker *et al.* 1991	db. pc	oral	stable-plaque/60	84	9*	1·6	1·0	+
Escobar *et al.* 1992	sb. pc	topical	stable-plaque/25	28	–*			+
Henneicke *et al.* 1993	db. Pc	topical	stable-plaque/52	56	–**			−
Soyland *et al.* 1993	db. pc	oral	stable-plaque/145	120	6**	3·1	1·9	−

[a] db = double-blind. sb = single-blind. pc = placebo-controlled.
[b] *Fish-oil preparations; **highly purified *n*-3-PUFA-ethylesters; ***cod-liver oil.
[c] + = improvement; − = no effect.

Table 2. Fatty acid composition of *n*-3- and *n*-6-lipid emulsions

Fatty acid (g/l)		Omegaven	Lipoven
Myristic acid	C14:0	4·6	–
Palmitic acid	C16:0	9·0	12·4
Palmitinoleic acid	C16:1n7	7·6	–
Stearic acid	C18:0	1·8	4·2
Oleic acid	C18:1n9	11·5	23·0
Linoleic acid	C18:2n6	2·8	52·9
Alpha-Linolenic acid	C18:3n3	1·7	7·6
Arachidonic acid	C20:4n6	1·5	–
Eicosapentaenoic acid	C20:5n3	21·1	–
Docosapentaenoic acid	C22:5n3	2·8	–
Docosahexaenoic acid	C22:6n3	21·5	–
Others		15·4	–

infusion regimens were restricted to rare irritations at the site of peripheral intravenous route. Fasting serum triacylglycerol concentrations decreased significantly in most patients after infusion of the *n*-3 emulsion, while serum cholesterol was unchanged.

Trial 1: A moderate improvement in clinical manifestations was noted in the *n*-6 group (changes in score systems between 16 % and 25 % from baseline within 10 days). In contrast, the severity of disease markedly decreased in all patients of the *n*-3 group, with improvement in all score systems ranging between 45 % and 76 % within 10 days ($P < 0{\cdot}05$ for each variable). The difference in response of the two regimens was evident within 4–7 days after onset of lipid infusion. A more than 10-fold increase in neutrophil EPA-derived 5-lipoxygenase product formation (LTB5, its omega-oxidation products, non-enzymatic degradation products of LTA5 and 5-hydroxyeicosapentaenoic acid) was noted in the *n*-3 group but not in the *n*-6 group. This increase in EPA-derived product formation was clearly evident on day 3 (first analysis after onset of infusion), progressed continuously to day 10, and was followed by a drop to baseline values within 30 days after termination of the infusion. Neutrophil PAF generation increased in the *n*-6 group but decreased in the *n*-3 group. Partial relapse phenomena were noted in some patients within 1–2 weeks after terminating the *n*-3 lipid infusions.

Trial 2: During the first treatment period PASI-Score dropped from 18·4 to 4·2. In addition, leukotriene (LT) generation of ionophore-stimulated neutrophils showed a more than 10-fold increase in EPA-derived lipoxygenase product formation. Probably because of a worse clinical condition in the second treatment period, the patient responded more slowly than during the first period (improvement of PASI from 22·2 to 8), and the increase of EPA-derived metabolites was more retarded.

Trial 3: The total PASI score decreased by $11{\cdot}2 \pm 9{\cdot}8$ in the *n*-3 and by $7{\cdot}5 \pm 8{\cdot}8$ in the *n*-6 group ($P{=}0{\cdot}048$). In addition, the *n*-3 group was superior to the *n*-6 group with respect to change in severity of psoriasis per body area, change in overall erythema, overall scaling and overall infiltration as well as change in overall assessment by the investigator and self-assessment by the patient. Response (defined as decrease in total PASI of at least 50 % between admission and last value) was seen in sixteen out of forty-three patients (37 %) under *n*-3 and nine out of forty patients (23 %) under *n*-6 fatty acid-based lipid emulsion. Within the first few days of *n*-3 lipid administration, but not in the *n*-6 supplemented patients, a significant increase in neutrophil LTB_5 and platelet TxB_3 generation and plasma-free EPA concentration occurred (Fig. 1a/b).

Discussion

A number of studies have evaluated the therapeutic benefit of *n*-3 fatty acids either using fish oil or highly purified *n*-3 fatty acid ethyl esters by the oral or topical route (Grimminger & Mayser, 1995). The present investigations were conducted to demonstrate the efficacy and safety of an *n*-3 fatty-acid-based lipid infusion in patients with acute-exanthematic and chronic plaque psoriasis. In contrast to oral *n*-3 fatty acid supplementation, intravenous infusion of EPA- and DHA-containing triglycerides was chosen to achieve substantial plasma levels of alternative precursor fatty acids within a short period of time.

n-3 Lipids caused a statistically significant larger decrease in the clinical symptoms of psoriasis compared with *n*-6 lipids, and a considerably higher response rate than infusion of *n*-6 lipids. In the first trial changes in score systems between 16 % and 25 % from baseline were noted within 10 days in the *n*-6 group and between 45 % and 76 % in the *n*-3 group (Grimminger *et al.* 1993*a*). The second trial showed that *n*-3 lipid infusions are successful even in relapsing psoriasis (Mayser *et al.* 1996). With response being defined as a decrease in total PASI between admission and last assessment of at least 50 % in the third trial 37 % were found to be responders in the *n*-3 lipid group and 23 % in the *n*-6 lipid group within a 14 day-treatment period (Mayser *et al.* 1998).

Data from both double-blind studies strongly suggest that differences between the two lipid infusion groups were due

Table 3.

Year	Clinical form	No. of patients	Days	Dose g/day EPA	Dose g/day DHA	Biochemical parameters determined
1990	Acute-exanthematic	20	10	2·1	2·1	EPA- and AA-derived 5 LO-products; PAF
1995	Acute-exanthematic	1	10	2·1	2·1	EPA- and AA-derived 5 LO-products
			15	4·2	4·2	
1996	Chronic-plaque	83	14	4·2	4·2	EPA- and AA-derived 5 LO-products; plasma FFA; TXB2/B3

DHA = docosahexaenoic acid.
The experimental procedures for determination of neutrophil-derived 5-LO products, PAF, plasma-free fatty acids and TXB2/B3 are described in detail in the publications by Hjorth *et al.* 1981, Grimminger *et al.* 1988*a*/*b*, Pace-Asciak, 1989, Grimminger *et al.* 1993*a*/*b* and Krämer *et al.* 1993.

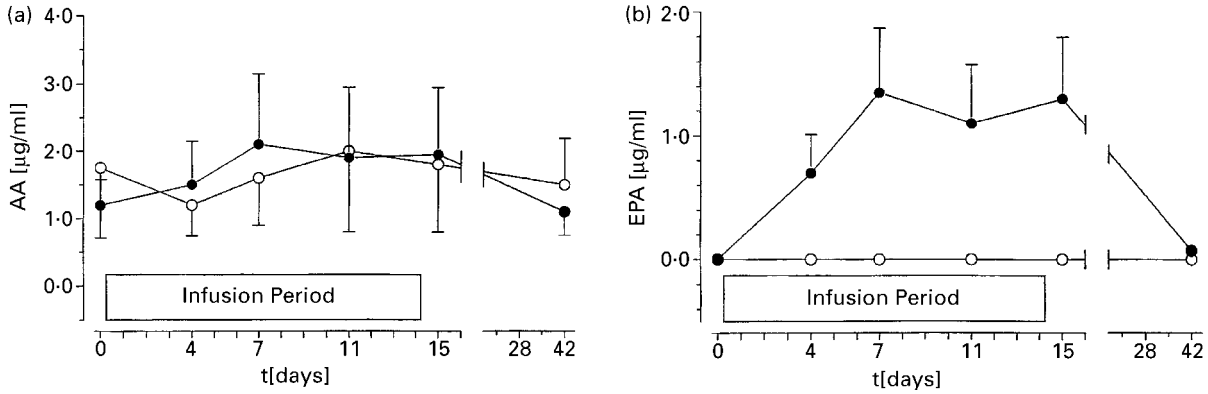

Fig. 1. Time course of plasma-free arachidonic (a) resp. eicosapentaenoic acid (b) during days 1–15, as well as 14 and 28 days after the infusion periods with *n*-6- (○) or *n*-3 (●)- lipid emulsion. Blood was collected immediately before onset of infusion. Data are given as µg/ml (mean +/− sem).

to an improvement in the *n*-3 lipid group rather than deterioration in the *n*-6 lipid group. It may even be speculated that intravenous *n*-6 fatty acid infusion caused some regression of the psoriatic lesions. Such findings might be related to the pharmacological effects of the high amount of linoleic acid in the *n*-6 lipid infusion, as previously discussed (Ruzicka & Groß, 1989). However, to support such speculation, an additional control group would be needed, which was excluded by the blinded protocol in both studies.

In all trials no severe adverse effects of the *n*-3 fatty acid-based preparation in the psoriatic patients were not noted. Laboratory variables remained in the normal range, and plasma triglyceride levels even decreased, which is in line with the well-established effects of *n*-3 lipids on lipid metabolism.

As previously described (Mascioli *et al.* 1989; Von Schacky & Weber, 1985), baseline plasma levels of EPA are low. A rapid increase in plasma-free EPA within the first days of *n*-3 lipid infusion was demonstrated in the third study. This finding signals rapid hydrolysis of the esterfied precursor: infusion of artificial lipid aggregates may activate endothelial lipoprotein lipase, including translocation of the enzyme from its cellular binding site into the vascular compartment (Yamazaki *et al.* 1991; Grimminger *et al.* 1992; Peterson *et al.* 1990). The increasing plasma lipolytic activity will then cause a rise in plasma-free fatty acids, which escape local cellular uptake mechanism. Thus, the kinetics and extent of plasma EPA increase observed in the third study exceed by far corresponding alterations in response to usual dietary fish oil uptake (Harris *et al.* 1988). Parallel with the plasma-free EPA increase, a rise of neutrophil LTB_5 generation and platelet TxB_3 formation occurred, indicating the influence of the alternative fatty acid precursor on the lipoxygenase and cyclooxygenase pathways. Notably, this shift to 5-series leukotrienes and 3-series Tx generation was observed upon *in vitro* challenge of neutrophils and platelets in the absence of plasma in the present study. These findings suggest that some EPA-containing membrane lipid pool(s), providing precursor fatty acids to the metabolic pathways of eicosanoid formation, may be rapidly regulated in exchange with plasma EPA. It remains speculative whether the generation of EPA-derived metabolites might even be markedly higher upon neutrophil and platelet stimulation with natural agonists in EPA-containing environments. For example, it is known that inflammatory agents occurring in psoriatic lesions, such as LTB_4 and platelet activating factor, critically depend on the presence of extracellular precursor fatty acid for induction of LT generation and PMN activation (Grimminger *et al.* 1992; Mahadevappa & Powell, 1989). In the presence of substantial microenvironmental concentrations of free EPA, neutrophil-keratinocyte cooperation in eicosanoid biosynthesis, suggested to be responsible for the high local concentrations of eicosanoids in psoriasis (Sola *et al.* 1992; Iversen *et al.* 1993), must be assumed to be shifted to the less potent and partially antagonistic EPA-derived metabolites.

It remains questionable whether skin lesions might improve even more impressively by infusion of higher *n*-3 lipid doses than those used in our trials, which are known to provide more elevated plasma-free EPA concentrations (Grimminger *et al.* 1993*b*). Furthermore it would be of interest whether comparable effects could be achieved by a once daily application, which would be optimal for outpatient therapy. In summary, intravenous *n*-3 lipid supplementation could widen the treatment options in acute-exanthematic and severe chronic-plaque type psoriasis with special emphasis to rotational therapeutic procedures and to combination regimens together with topical anti-psoriatic compounds such as dithranol or vitamin D_3 analogues.

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