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Comparative Epidemiological Study in Patients with Rheumatic Diseases Illustrated in an Example of a Treatment with Non-Steroidal Anti-inflammatory Drugs versus an Oral Enzyme Combination

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Summary

To establish the safety and efficacy of an oral enzyme-combination product (OE; Phlogenzym®, containing trypsin, bromelain and rutin) in the treatment of rheumatic diseases a retrolective cohort study with parallel groups was undertaken as an epidemiological study, in which the enzyme combination was compared with non steroidal anti-inflammatory drugs (NSAID). Data of 3326 patients treated for rheumatic diseases between January 1993 and the end of March 1995 were registered by 380 physicians. From the patient file age, gender, indication for treatment (diagnostic group), anamnestic data (especially pre-treatment), complaints at the beginning and end of treatment, treatment duration, prescribed drugs (OE, NSAID), additional treatment and adverse events were transferred into case report forms (CRFs). The quality of the data was monitored and additionally checked by internal and external quality audits. Included in the efficacy analysis were 2139 patients which were treated either only with OE or only with NSAID and could be classified unambiguously into one of the following diagnostic groups: joint diseases, spinal diseases, rheumatic soft tissue diseases. As clinically relevant and reliably evaluable criterion freedom from rheumatic complaints at the end of treatment was considered. For evaluation of safety the documented adverse events of all patients were considered. Two thirds of the OE patients received the recommended dose of 6 tablets/day, taken for 23 to 35 days. The respective mean values for NSAID patients were 16 to 25 days, and the patients were treated with the recommended symptomatically effective doses of NSAID.

As the allocation of the compared treatment options (OE or NSAID) to the patients was not randomized, a mixing of treatment effects with other factors cannot be excluded. For adjustment of these confounding factors two methods were applied: a) logistic regression of the relative ratio of the main criterion and all confounding factors and b) stratification of data according to the propensity score i.e. the probability of a treatment with OE. Both methods yielded similar results: A 50 % higher success rate can be expected in total for OE than for NSAID at comparable initial and treatment situations (95 % confidence interval with logistic regression = 1,218-1,96, with stratification according to propensity score = 1,16-1,84). As significant negative indicators for response age over 50 years, pre-treatment with antirheumatic

or analgetic drugs, treatment duration more than 30 days and joint diseases or fibromyalgias could be revealed. Since there was no interaction between these indicators and the type of treatment also in patients presenting with these indicators a treatment success (freedom from symptoms) with OE can be expected with a higher probability than with NSAID.
OE were well tolerated showing much less adverse events when compared with conventional doses of NSAID.

Zusammenfassung

Vergleichende epidemiologische Studie bei Erkrankungen des rheumatischen Formenkreises am Beispiel der Therapie mit nichtsteroidalen Antiphlogistika versus einem oralen Enzymkombinationspräparat

Zum Nachweis der Anwendungssicherheit und Wirksamkeit eines oralen Enzymkombinationspräparats (OE; Phlogenzym®, enth. Trypsin, Bromelain und Rutin) bei Erkrankungen des rheumatischen Formenkreises wurde als epidemiologische Studie eine retrolektive Kohortenstudie in parallelen Gruppen durchgeführt, in der das Enzymkombinationspräparat gegen nichtsteroidale Antirheumatika (NSAR) verglichen wurde. Bei 380 Ärzten wurden die Daten von 3326 Patienten erfaßt, die zwischen Januar 1993 und Ende März 1995 wegen rheumatischer Beschwerden behandelt wurden. Aus den Patientenakten wurden Alter, Geschlecht, Behandlungsindikation (Diagnosegruppe), anamnestische Befunde (insbesondere Vorbehandlung), der Beschwerdestatus zu Beginn und am Ende der Behandlung, die Behandlungsdauer, die verordneten Medikamente (OE, NSAR), Zusatzbehandlungen und unerwünschte Ereignisse ermittelt und in vorbereitete Prüfbögen übertragen. Die Qualität der erfaßten Daten wurde durch Monitoring und zusätzliche interne und externe Qualitätsüberprüfungen kontrolliert. Zur Evaluation der Wirksamkeit von OE wurden die Daten der 2139 Patienten verwendet, die entweder nur mit OE oder nur mit NSAR behandelt wurden und deren Behandlungsanlaß eindeutig einer der drei Diagnosegruppen Gelenkerkrankungen, Wirbelsäulenerkrankungen, oder weichteilrheumatische Erkrankungen zugeordnet werden konnte. Als klinisch relevante und zuverlässig den Krankenakten zu entnehmende Zielgröße wurde die Beschwerdefreiheit am Ende der Behandlung herangezogen. Die Bewertung der Anwendungssicherheit erfolgte mit den erfaßten unerwünschten Ereignissen der Gesamtstichprobe. Zwei Drittel der Patienten der OE- Gruppe erhielten die empfohlene Tagesdosis von 6 Tabletten, die, abhängig von der Diagnose, zwischen 23 und 35 Tagen eingenommen wurden. Die entsprechenden Mittelwerte für die NSAR Gruppe waren 16 bis 25 Tage, wobei die empfohlenen, üblicherweise symptomatisch wirksamen Dosierungen von NSAR verwendet wurden.
Da die Zuteilung der zu vergleichenden Behandlungen (OE oder NSAR) zu den Patienten nicht randomisiert erfolgte, ist eine Vermengung des Behandlungs-Einflußes mit anderen Einflußfaktoren auf die Zielgröße nicht auszuschließen. Zum Ausgleich dieser Vermengungen wurden zwei Verfahren angewandt: a) logistische Regression der relativen Quote der Zielgröße zu allen Einflußfaktoren und b) Schichtung der Daten nach dem Zuteilungsscore (propensity score), d. h. der Wahrscheinlichkeit für eine OE-Behandlung. Beide Verfahren führten zu einem ähnlichen Ergebnis: Insgesamt kann bei vergleichbarer Ausgangs- und Behandlungssituation mit OE eine um ca. 50 % höhere Erfolgsquote erwartet werden als mit NSAR (95 %-Konfidenzintervall bei logistischer Analyse: 1,21–1,96; bei Schichtung: 1,16–1,84). Als signifikante negative Indikatoren für den Behandlungserfolg erwiesen sich: Behandlungsdauer über 30 Tage, Behandlung durch Orthopäden, Gelenkerkrankungen oder Wibelsäulenerkrankungen, Vorbehandlung mit Antirheumatika oder zusätzlicher Analgetikabedarf. Da aber keine Wechselwirkung zwischen der Behandlungsart und diesen Indikatoren bestand, ist auch bei Vorliegen dieser Indikatoren unter OE mit größerer Wahrscheinlichkeit ein Behandlungserfolg (Beschwerdefreiheit) zu erwarten als unter einer Behandlung mit NSAR.
Die Anwendungssicherheit des Enzympräparates ist als problemarm zu bewerten. Im Vergleich zu NSAR, die in den üblichen und therapeutisch wirksamen Dosierungen eingesetzt wurden, wiesen OE ein deutlich günstigeres Nebenwirkungsprofil auf.

Key words Anti-inflammatory drugs, non-steroidal · Logistic regression · Propensity score · Phlogenzym®, comparative epidemiological study · Proteolytic enzymes · Rheumatic diseases

1. Introduction

Therapeutic use studies and epidemiological observational studies are winning a greater significance in re-registration or in the investigation of the efficacy and safety of drugs that are already on the market. In the guideline 1999/83/EC of the Commission of the European Community dating 8th September 1999 it was determined that: "In particular the clarification that bibliographic referrals to other information sources (for example investigations after circulation, epidemiological studies or studies implemented with similar products) and not only trials and investigations can be used as valid proof of the safety and efficacy of a product, when the applicant sufficiently explains and gives the reason why this particular information source is quoted" [1]. It therefore follows that for the proof of safety and efficacy of a drug whose ingredients are generally used medicinally that the results of appropriate, carefully planned and implemented epidemiological observational study are suitable.

1.1.Concept of the cohort study

One type of observational study which is particularly suited to investigate the proof of efficacy and safety in drugs, is the epidemiological cohort study (comparative cohort study) [2–4]. In this type of study a representative and sufficiently large random sample is recruited out of physicians practices, clinics or other therapeutic centres that treat patients with the indications for which the drug to be tested is prescribed. The selection of patients can either be a retrospective or by a retrolective study design (with data collection in a forward direction, but with a retrospective starting point)[5] or by a prospective study design. The centres should use not only the test preparation but other preparations on the market which can serve as a control treatment. In accordance to the characteristics of epidemiological observational studies the treating physician will not be influenced in regards to his decision for an indication and in his choice and the implementation of a therapy in the individual cases. It will be carefully registered with which patient what preparations were administered and how the course of illness develops under the therapy.

The careful "planning and conduct of the study" so as an "evaluation of the results according to the state of the scientific knowledge of the disciplines involved" [6] is an indispensable requirement for the validity of the study. Before study commencement a study protocol must be available in which the study endpoints, the study design (selection of centres, inclusion and exclusion criteria for the patients, capture and documentation of the findings, definition of the outcome variables, control of the findings) and the evaluation strategy are clearly and comprehensively presented. The quality of the study strongly depends on the representative selection of the participating centres, the as complete as possible screening of all patients who come for treatment with the stipulated indications within the given period of time (or, with retrolective registration, came for treatment) as well as the most complete as possible and controlled documentation of the required findings in a standardised form (anamnesis, status, applied therapies, concomitant therapies, course of disease, special events, side effects) [3, 5, 7, 8].

The free choice of the test and comparison treatment has turned out to be a special problem in the evaluation and assessment of the results [9]. It cannot be assumed that this choice is carried out independently of the special characteristics of the patients (past medical history, initial condition, habits and others). Besides, the additional treatment measures might not be independent of the choice of the primary drug used. It must be conclude that the patient group treated with the test drug and the group treated with the comparator preparation is not balanced in regards to these characteristics. Therefore, a crude comparison of the treatment effects between both groups can be biased through these characteristics (a mix of treatment effect and other factors, e.g. potential confounders). The primary aims of the evaluation and assessment of the results must therefore be, the differences in both the treatment groups must be documented as exactly as possible, the influence of the different characteristics (potential confounders) on the treatment results must be recorded and, with suitable methods, the difference of the treatment results must be adjusted with respect to the influence of confounders. In this paper two methods (multiple logistic regression and stratification according to a propensity score) are applied with which such an unbiased comparison can be performed [9, 10].

For the examination of efficacy and safety of a therapy with an oral enzyme combination preparation[1)] (OE) in rheumatic diseases, a retrolective cohort study was carried out. The enzyme preparation examined has been available since 1991 and is used in the therapy of (among others) diverse rheumatic diseases whereas in the foreground is the treatment of the inflammatory condition.

Drugs with a high content of proteolytic enzymes have traditionally long been used in a line of complaints and diseases. The implementation in modern medicine is, on the one side, based on clinical studies, and on the other side furthermore on empirical knowledge of the users. One of the most essential areas for the application of enzyme preparations are rheumatic diseases [11–13].

2. Material and methods

2.1. Planning of the study and selection of study centres

Study protocol and standardised case report form (CRF) were developed in accordance to the usual documentation procedures in general practice, and

[1)] Phlogenzym®, containing trypsin, bromelain, and the flavonoid rutin; manufacturer: Mucos Pharma GmbH & Co., Geretsried (Germany).

a comprehension test of the CRF in a series of practices (general practitioner, internist, physician for natural healing) was carried out. For the acquisition of the study centres firstly a random sample out of a commercial physicians address bank was selected and with these physicians a standardised survey was carried out. An analysis of the results showed that only about 10 % of the destined physicians had prescribed oral enzymes in 1995 and thus being in the position of documenting the required 5–10 patients treated with this preparation. Therefore, the acquisition of the study centres was carried out by accordingly instructed and schooled sales representatives of the sponsor. Following instruction, these sales representatives were also appointed to carry out the monitoring of the study. The acquisition of the centres was carried out as follows: The external monitors should ask all physicians in the course of their routine visits about the study independent of whether they prescribe oral enzymes or not, therefore only being eligible to enter patients into the control group. The avoidance of a selection bias through this procedure was tested through a sensitivity analysis, the result being that none of the physicians had a preference for one or the other therapy.

2.2. Selection of patient data

From the physicians medical records a complete documentation of the treatment data of all patients who complied with the stipulated inclusion and exclusion criteria in the study protocol, whereas through the number of CRFs handed out a distribution of 2 to 1 in favour of OE versus NSAID was striven for. The inclusion criteria were: age between 18 and 80 years, degenerative, activated inflammatory joint diseases, degenerative, activated inflammatory diseases of the spinal column, fibromyalgia, medical treatment between January, 1993 and the end of March, 1995 (if there were multiple treatments within this period of time the first treatment was selected for the study) and the treatment with OE or NSAID for at least one day. The exclusion criteria were therapies with other enzyme preparations, corticosteroids, immune-suppressants, immunomodulators, cytostatic agents, gold salts or d-penicillamin within the last three months, malign tumours, psychoses with restricted sound of mind, other autoimmune diseases other than rheumatic disease as well as manifest infectious diseases. In the case that patients were treated for a rheumatic disease before the recorded period of time this was recorded under anamnestic data. As study data, only the results of that treatment were evaluated which took place within the stipulated period of time. The concomitant use of analgesics (e.g. paracetamol) was allowed and it's usage documented.

2.3. Data capture and data processing

The patient's data was extracted out of the medical records by the physician and, in accordance with the written and oral instructions, transferred into the CRFs. The completed CRFs were collected by the study monitors or sent directly to the contract research organisation to be examined for completeness and data plausibility. With missing essential data or comprehension problems a second monitoring was implemented in the concerning centres. The usual procedure was a query by mail or by telephone, and in only a few cases by personal contact through a study monitor. After coding data were entered into an SPSS-database. With the original CRFs and the print outs of the computer generated CRFs out of the database, the correctness of the data transfer was verified and finally an electronic plausibility and quality control was undertaken. An independent auditor controlled the presence of all original CRFs, their print outs and all the alterations from the original data. In a 10 % random sample, the correctness of the coding as well as the data transfer from the original CRFs onto the data carrier were controlled ("indoor audit"). In an independent audit of study centres a 5 % random sample of the CRFs were controlled through interview technique.

3. Results

3.1. Study centres, patients and reasons for treatment (diagnosis group)

Data from a total of 3326 patients (total sample) was gathered from 380 physicians (Fig. 1). Included in these were 267 general physicians and general practitioners, 45 physicians with the additional

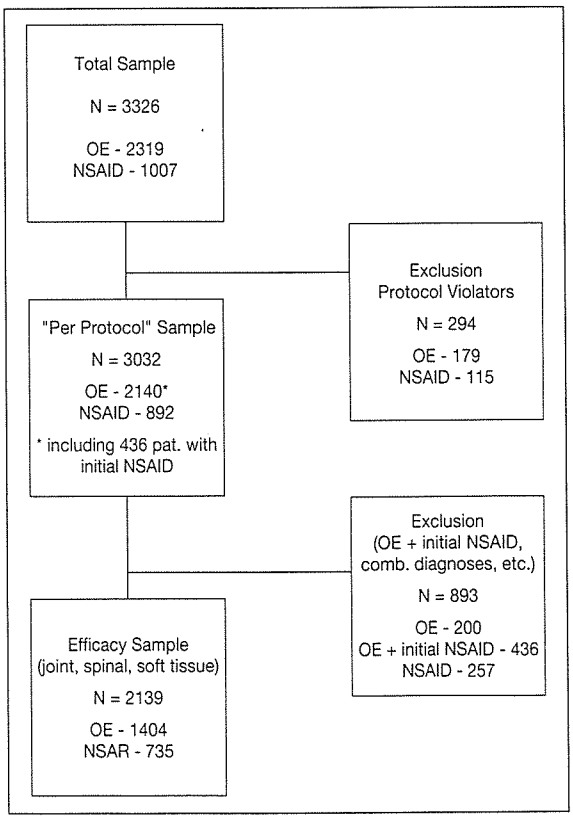

Fig. 1: Definition of total sample (safety) and of study sample (efficacy).

Table 1: Number of patients for the individual diagnostic resp. treatment groups.

Diagnostic group	Treatment			Total
	OE	NSAID	OE/ NSAID[a)]	
Joint diseases	370	209	80	659
Spinal diseases	321	250	79	650
Fibromyalgia	106	45	24	175
Other soft tissue diseases	646	254	185	1085
combined diagnoses	220	131	64	415
Trauma	39	2	3	44
Missing	2	1	1	4
Total	1704	892	436	3032

[a)] NSAID mainly initially in the first days of treatment.

qualification for natural healing, 24 internists and 37 orthopaedists. With 7 physicians the statement as to subject area was missing. Safety analysis was carried out within the total sample.

For the evaluation of efficacy, in a first step 294 patients were excluded who did not comply with the inclusion and exclusion criteria. In the main they were patients who exceeded the required age, with forbidden concomitant therapy as well as missing statements regarding the length of therapy which could not be ascertained later. Out of the remaining 3032 patients, 1704 were treated solely with OE, 892 solely with NSAID and 436 with both so that the aimed distribution in the random sample was achieved with about double the number of OE patients. The reasons for treatment were documented in the medical history. These reasons were classified into rheumatic disease (sub)groups: joint diseases, spinal diseases, fibromyalgia or other soft tissue diseases (e.g. epicondylitis, tendovaginitis, shoulder arm syndrome) and different combinations out of these major diagnosis groups. The distribution of the patients into the different treatment and diagnosis groups are shown in Table 1. The most frequent diagnosis group were "other soft tissue diseases" followed by joint diseases and spinal diseases. In addition, 44 cases of trauma were presented. The distribution quotient of OE/ NSAID was more than 2:1 in fibromyalgia and other soft tissue diseases, 1.8:1 in joint diseases, and 1.3:1 in spinal diseases.

To be able to obtain explicit results on treatment effects in both of the treatment groups only those patients were included in the evaluation who were treated either with NSAID or with OE. These were 2596 patients. Out of this group those patients were excluded who could not be definitely relegated to one of the three diagnosis groups: joint diseases, spinal diseases and soft tissue rheumatism (including the diagnoses fibromyalgia and other soft tissue diseases). The patient group "trauma" was excluded because of its small sample size. Therefore, altogether the data of 395 patients were excluded. Furthermore, those patients were excluded whose statements as to sex (5 patients), age (28 patients), or speciality areas of the physician (29 patients) were missing. Therefore, a remaining total of 2139 patients was included in the analysis (efficacy sample).

3.2. Therapies/therapy groups

Out of the 2139 patients, 1404 (65.6 %) were treated with OE and 735 (34.4 %) with NSAID as a main therapy. The NSAID applied are shown in Table 2 (multiple nominations are possible). The average daily dosage of the three most commonly prescribed NSAID were diclofenac 130 mg, piroxicam 27 mg and ibuprofen 1220 mg.

The analysis of the OE applications showed that approximately two thirds of the patients (68 %) were treated with manufacturer's recommended dose of 6 tablets daily. Only 5 % of the patients received a lower dose of 2 to 5 tablets. In 11 % of the patients 9 tablets daily were prescribed. The remaining patients received higher doses which in individual cases reached the amount of 45 tablets daily.

The application and the observation duration respectively varied in length in both the therapy groups, and within the treatment groups it varied in length also between the individual diagnoses. Generally, the NSAID patients were treated for a shorter period in time than the OE patients The average treatment duration was 35 days for the OE group with joint diseases, in spinal diseases 31 days, and in soft tissue rheumatism 23 days. The corresponding values for the NSAID group were 25, 16 and 16 days.

Because the test therapy and the NSAID control therapy were not randomly assigned to the patients, differences in the patients' characteristics between both therapy groups were to be expected. Table 3 shows the distribution of the most important characteristics of both therapy groups.

In regards to sex and age there were no relevant differences (average age: NSAID 51 years, OE 50 years; female representation: NSAID 48.6 %, OE 59.5 %). Patients with spinal diseases were more often treated with NSAID and patients with other soft tissue diseases more often with OE. There was a relevant difference in the pre-treatment with antirheumatics and/or analgesics. 16.7 % of the patients treated with NSAID had undergone such a pre-treatment and 32.6 % of the patients treated with OE.

The percentage of patients who did not receive a concomitant treatment was 36.9 % in the NSAID group and 47.9 % in the OE group. Additional analgesics were given in 15.6 % of the NSAID group and in 8.3 % of the OE group. The duration of therapy was shorter in the NSAID than in the OE group (median value NSAID 20 days, OE 30 days). The distribution into the specialist areas of the treating physicians differed predominantly in the physicians for natural healing who were nearly twice as often represented in the OE group than in the NSAID group.

Table 2: NSAID used (multiple nominations possible).

Drug	Diagnostic group			
	Joint diseases	Spinal diseases	Soft tissue	Total
Diclofenac	144	162	176	482 (66 %)
Piroxicam	26	43	47	116 (16 %)
Naproxen	1	3	6	10 (1 %)
Ibuprofen	29	40	60	129 (18 %)
Indometacin	10	8	10	28 (4 %)
Acetylsalicylic acid	6	8	13	27 (4 %)
Others	7	2	7	16 (2 %)

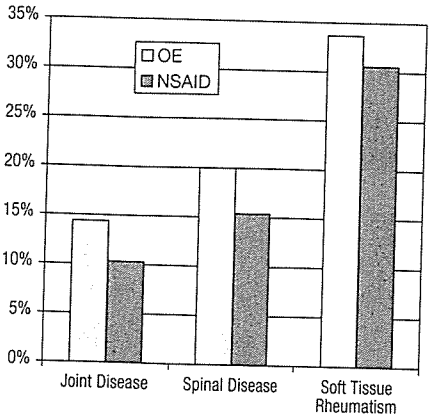

Fig. 2: Frequency of "symptom free" patients in the resp. treatment groups, separate for the diagnostic groups.

3.3. Symptoms

Out of the medical records, the severity of 17 of the examined diagnosis' typical symptoms were determined at the commencement and termination of therapy and coded as follows: 0 (= none), 1 (= mild), or 2 (= severe). These were the following complaints: morning stiffness, fatigue/exhaustion, arthralgia at rest, arthralgia when active, tender joints, swelling of joints, restriction in joint mobility, back-pain at rest, back-pain when active, restriction in spinal column mobility, myalgia and tenalgia at rest, myalgia and tenalgia when active, muscle- and tendon tendorness, soft tissue swelling, sleep disorders due to pain, being bedridden, oedema. At the commencement of treatment all the patients had at least one of these symptoms. A clinically relevant variable at an individual level is therefore the evaluation of freedom of complaints at the termination of therapy. In the NSAID group at the termination of therapy 20.0 % of the patients were free of complaints, and in the OE group 25.7 %. The crude odds ratio, e.g. the relationship of patients free of complaints to patients with complaints in the OE and NSAID groups, was 1.384 with a 95 % confidence interval ranging from 1.111 to 1.720. The portion of complaint free patients in the individual diagnosis groups (separated according to therapy groups) is displayed in Fig. 2. The portion of complaint free patients was largest with 33 % in the diagnosis group "soft tissue rheumatism" and the smallest with 13 % in the diagnosis group joint diseases. In all diagnosis groups at the termination of therapy, there were more com-

Table 3: Distribution of the most important characteristics of both treatment groups.

		OE		NSAID		Total	
		n	%	n	%	n	%
Total		1404	100	735	100	2139	100
Sex	female	836	59.5	357	48.6	1193	55.8
	male	568	40.5	378	51.4	946	44.2
Age	up to 50 years	728	51.9	350	47.6	1078	50.4
	above 50 years	676	48.1	385	52.4	1061	49.6
Diagnosis	joint diseases	355	25.3	203	27.6	558	26.1
	spinal diseases	315	22.4	241	32.8	556	26.0
	fibromyalgia	104	7.4	45	6.1	149	7.0
	other soft tissue diseases	630	44.9	246	33.5	876	41.0
Pre-treatment with anti-rheum./analgesics	no	946	67.4	612	83.3	1558	72.8
	yes	458	32.6	123	16.7	581	27.2
Concomitant treatment	none	672	47.9	271	36.9	943	44.1
	antirheumatics/analgesics	620	44.2	391	53.2	1011	47.3
	others	112	8.0	73	9.9	185	8.6
Additional analgesics	no	1288	91.7	620	84.4	1908	89.2
	yes	116	8.3	115	15.6	231	10.8
Duration of treatment	1–14 days	300	21.4	302	41.1	602	28.1
	15–28 days	421	30.0	188	25.6	609	28.5
	29-56 days	339	24.1	112	15.2	451	21.1
	> 56 days	344	24.5	133	18.1	477	22.3
Investigator's speciality	general practitioner	936	66.7	517	70.3	1453	67.9
	add. qual. natural healing	228	16.2	67	9.1	295	13.8
	internist	73	5.2	48	6.5	121	5.7
	orthopaedist	167	11.9	103	14.0	270	12.6

Table 4: Evaluation of efficacy and tolerability of the applied therapy by the investigator.

		OE		NSAID		Total	
		n	%	n	%	n	%
Total		1404	100	735	100	2139	100
Efficacy	free of symptoms	561	40.0	201	27.3	762	35.6
	much better	667	47.5	324	44.1	991	46.3
	slightly better	121	8.6	150	20.4	271	12.7
	unchanged	54	3.8	57	7.8	111	5.2
	worse	1	0.1	3	0.4	4	0.2
Tolerability	excellent	1224	87.2	221	30.1	1445	67.6
	good	164	11.7	278	37.8	442	20.7
	moderate	11	0.8	175	23.8	186	8.7
	unsatisfactory	2	0.1	45	6.1	47	2.2
	poor	3	0.2	16	2.2	19	0.9

plaint free patients with the OE therapy than with the NSAID therapy.

3.4. Evaluation of efficacy and tolerability through the physician

For each patient the physician evaluated the applied therapy for tolerability and efficacy. The results are displayed in Table 4. The physicians evaluated much more patients as being "symptom free" than it could be ascertained through the statements about complaints in the medical record. Also, according to the physicians judgement there were clearly more patients symptom free after the OE therapy than after the therapy with NSAID.
The tolerability of the OE therapy was evaluated with 87.2 % as being very good, whereas the NSAID therapy was only evaluated with 30.1 % as being very good.

3.5. Safety

In Table 5 the adverse events (AE) for the total sample are displayed according to organ systems. In the OE group 68.5 % of the AE were evaluated as being mild, 21.0 % as moderate and 10.5 % as severe. The corresponding pattern in the NSAID group is 43.2 %, 43.5 % and 8.3 %. The patients statement as to the duration of the AE in the OE group were: up to 5 days 60 % and up to 10 days 18 %, whereas a longer duration was recorded in the NSAID group (up to 5 days: 50 %; up to 10 days: 33 %). Actions taken were reported in 50 patients in the OE group and 167 patients in the NSAID group: In 22 patients OE were discontinued, in 14 patients the OE dosage was reduced and in 14 patients other measures were tried e.g. change in diet. In the control group, in 10 patients following a preliminary dosage reduction the NSAID were discontinued, in 137 patients gastroprotective drugs were prescribed and in 20 patients other measures were tried, e.g. change in diet.

3.6. Balance of inhomogeneity of the treatment groups with logistic regression

As the treatment allocation (NSAID or OE) was not randomised, the crude estimated difference in treatment outcome (e.g. odds ratio for freedom of complaints) is potentially biased through additional influence factors (confounders). A method to assess for and remove such a bias in regards to a binary endpoint is the logistic regression [10].
Efficacy outcome variable is the probability p of being symptom free at the termination of therapy. For the relationship between this probability and a set of explanatory variables a logistic function is assumed; i.e. the logarithm of the odds for symptom freedom, log(P/(1-P)) will be set as a linear function of the different explanators:

$$\log(P/(1-P)) = b_o+b_1x_1+...+b_kx_k$$

where x_i symbolises the value of the explanator i and the coefficient b_i shows by how much the logarithm of the ratio changes (log-odds) when the value of x_i is increased by one unit. The value $\exp(b_i)$ is the odds ratio of the explanator x_i when its value increased by one unit and all the other explanators are set on their reference value. It characterises the influence of the value i on the freedom of symptoms, adjusted for all other covariates. For the

Table 5: Number and type of adverse events for the total sample.

Adverse events (AE)		OE		NSAID	
		n	%	n	%
Total		2319	100	1007	100
Patients	with AEs	89	3.84	276	27.4
	> 1 AE	15	0.65	36	3.6
	gastro-intestinal AEs	81	3.5	262	26.0
	discontinuation because of AEs	22	0.95	10	1.0
Organ system (WHO)	gastro-intestinal system disorders	94		286	
	skin and appendages disorders	2		8	
	central and peripheral nervous syst. disorders	3		9	
	heart rate and rhythm disorders			1	
	psychiatric disorders			3	
	metabolic and nutritional disorders			1	
	general disorders	6		7	

Table 6: Result of logistic regression analysis: adjusted odds ratios for freedom of symptoms for individual patient's and treatment characteristics.

Indicator for success of treatment	Rel. quote $\exp(b_i)$	95% Confidence interval	p
Treatment with OE	1.538	1.210–1.966	<0.001
Age above 50 years	0.531	0.423–0.667	<0.001
Sex male	1.004	0.809–1.246	0.970
Duration of treatment >28 days	0.386	0.304–0.490	<0.001
Speciality: natural healing	0.994	0.730–1.354	0.971
Speciality: internal medicine	0.591	0.348–1.003	0.051
Speciality: orthopedics	0.544	0.381–0.777	0.001
Diagnosis: joint diseases	0.476	0.353–0.643	<0.001
Diagnosis: spinal diseases	0.629	0.479–0.825	0.001
Pre-treatment with antirheum./analget.	0.660	0.502–0.867	0.003
Concomitant therapy: antirheum./analget.	1.101	0.886–1.369	0.386
Additional analgetics	0.606	0.405–0.907	0.003

tested variables, the logistic regression analysis for freedom of symptoms at the termination of treatment revealed the adjusted odds ratios displayed in Table 6.

The adjusted odds ratio for freedom of symptoms in the OE therapy (relative to the NSAID therapy) amounts to 1.538 (95 % CI: 1.210-1.955). This means that with an OE treatment the chance of getting free of symptoms at the end of treatment was about 50 % higher than with NSAID. The difference is statistically highly significant.

Table 6 shows that some other patients' and treatment characteristics can significantly influence the outcome of the therapy (freedom of symptoms). As in the calculation of the odds ratio of an explanatory all other parameters are set to their reference value, the odds ratio for freedom of symptoms for OE is not biased through confounding effects of the covariates.

Further important and statistically significant indicators for the success of the treatment (e.g. freedom of symptoms at the termination of treatment) are: age (in patients over 50 less success than with patients under 50), duration of therapy (in a lengthy duration of therapy less success than with a shorter one), the speciality area of the physician (orthopaedists have less success than other specialists), the diagnosis group (in joint diseases and spinal column diseases less success than with soft tissue rheumatism), the pre-treatment with anti-rheumatics (with pre-treatment less success than without pre-treatment), and an additional treatment with analgesics (with additional therapy less success than without an additional therapy). The patients sex and a concomitant therapy had no significant impact on the patient outcome.

The assessment regarding the presence of interactions (effect modifier) between the variable "therapy group" and additional explanators (in particular diagnosis, age, and pre-treatment) did nor reveal any significant interactions. Thus it can be demonstrated that, independent of other explanators, with a therapy with OE a 50 % higher odds of symptom free patients is expected than with an NSAID treatment.

3.7. Equalization of inhomogeneity through stratification according to the allocation score (propensity score)

In observational studies, the allocation of OE treatment or NSAID treatment to the patients is a random event whose probability (in general depends on characteristics $x_1,...x_k$ of the patients or the physician: $\pi = \pi(x_1,...x_k)$. This probability of obtaining a test treatment when the characteristics $x_1,...x_k$ are present is named a propensity score [14, 15]. In controlled studies with randomised allocation, the probability π of obtaining a test treatment does not depend on the characteristics $x_1,...x_k$ but is the same for every patient (e.g. 50 % for a 1:1 randomisation). In observational studies this independence is generally not given. The allocation score as a function for characteristics can be estimated with a logistic regression.

Patients who have approximately the same propensity score, are similar in regards to the characteristics which formed this score, indifferent to whether they were treated with test therapy or the control therapy [14, 15]. This can be gathered from Table 7, in where the frequency of some treatment characteristics can be compared in which both of the treatment groups differ mostly, each within the strata of similar values of the allocation scores between both treatment groups. It is for example a pre-treatment (in the cohort at NSAID: 16.7 %, OE: 32.6 %). Within the strata the frequency of a pre-treatment is very similar in both treatment groups and ranges from 3.9 % and 0 % resp. in the stratum < 0.4 up to about 60 % in the stratum > 0.8. It is similar for patients with a concomitant therapy where the frequency for OE was 52.1 % and for NSAID 63.2 % and was reduced from about 80 % to about 40 % with an increasing allocation score.

The statements in Table 7 characterise the allocation score, i.e. the probability of an OE treatment and allow a conclusion as to the allocation mechanisms. Patients without an anti-rheumatic pre-treatment but with a concomitant medication and analgesics, joint or spinal disease and on the whole a shorter period of treatment were more likely to be treated with NSAID, whereas patients with an anti-rheumatic pre-treatment but without a concomitant therapy and additional analgesics with soft tissue rheumatism were most likely treated with OE.

One can assume that within a stratum the odds ratio for the therapy outcome (freedom of symptoms) is widely unbiased through confounding. In the case of the strata homogeneity in regards to the odds ratio (this means that although the rates of the symptom free patients differ within the strata, the expected odds ratios are the same), the estimates obtained within the strata can be combined with the method according to Mantel-Haenszel, resulting in an unbiased common estimate [10, 16].

Table 7: Comparison of the frequency of some important treatment characteristics in propensity score classes.

Propensity score	Characteristics	OE (%)	NSAID (%)
< 0.4	pre-treatment	0.0	3.9
	concomitant therapy	81.5	80.3
	additional analgetics	37.0	36.8
	soft tissue rheumatism	13.0	8.6
	duration of therapy >28 days	7.4	9.9
0.4 to 0.6	pre-treatment	9.6	6.5
	concomitant therapy	68.8	71.6
	additional analgetics	15.2	12.6
	soft tissue rheumatism	45.0	36.4
	duration of therapy >28 days	22.0	27.6
0.6 to 0.8	pre-treatment	24.1	21.2
	concomitant therapy	53.2	49.6
	additional analgetics	7.3	9.3
	soft tissue rheumatism	51.3	53.3
	duration of therapy >28 days	48.3	45.1
> 0.8	pre-treatment	64.1	63.2
	concomitant therapy	36.2	43.4
	additional analgetics	1.6	3.9
	soft tissue rheumatism	63.4	68.4
	duration of therapy >28 days	71.7	61.8

Table 8: Frequency of symptom free patients on OE or on NSAID and estimates for the odds ratios.

Propensity score	Treatment	Patients	"Free of symptoms"	Relative quote	95% Confidence interval
< 0.4	OE	54	15 (28 %)	1.631	0.794–3.351
	NSAID	152	29 (19 %)		
0.4 to 0.6	OE	282	85 (30 %)	1.867	1.249–2.789
	NSAID	261	49 (19 %)		
0.6 to 0.8	OE	634	170 (27 %)	1.272	0.899–1.801
	NSAID	246	55 (22 %)		
> 0.8	OE	434	91 (21 %)	1.175	0.629–2.194
	NSAID	76	14 (18 %)		

Table 8 shows the total number and the number of symptom free patients in the OE and NSAID groups for every stratum of the allocation scores and the resulting estimates for the odds ratios with their 95 % confidence intervals.

The Zelen-test for homogeneity of the strata (using the program StatXact® 4) showed no significant heterogeneity (p = 0.457) [17]. Thus, an underlying common odds ratio over the strata can be assumed. According to the Mantel-Haenszel method a common estimate of 1.461 (95 % confidence interval: 1.160 to 1.840) was calculated. The stratification of the patients according to the propensity score to balance the inhomogeneity of the treatment groups and the estimation of odds ratio in accordance to the Mantel-Haenszel method lead to similar result as the logistic regression. The odds of symptom free patients in the OE group is expected to be 40-50 % larger (95 % confidence interval of 16 % to 84 %) than with the NSAID therapy. The difference between both therapies is statistically highly significant. With the two different methods, therefore, a good balance in inhomogeneity and therefore an unbiased comparison of the treatment results between the test and control groups could be achieved which lead to practically the same results.

4. Discussion

The results show that with the retrolectively collected data of the cohort study, not only statements regarding safety and efficacy of the OE treatment in rheumatoid diseases can be revealed, but also information regarding application patterns in the practice. In the subdivision of the reasons for treatment into the three diagnosis groups joint diseases, spinal diseases, and soft tissue rheumatism it showed that OE in comparison to NSAID was prescribed relatively more often in soft tissue rheumatism than in joint and spinal diseases. Physicians for natural healing prescribed OE more often than physicians with other speciality areas. Patients treated with OE were more often (33 %) pre-treated with anti-rheumatics/analgesics than the patients treated with NSAID (17 %). This could be explained by the fact that within the patients treated with OE there was a higher percentage of patients previously unsuccessfully treated with other anti-rheumatics. A concomitant treatment and additional analgesic therapy were carried out less often in the patients who were treated with OE than in patients treated with NSAID. This could be a hint of the better efficacy of an OE therapy or could be the result of differences in basic data and treatment conditions between the OE or the NSAID treated patients. Such structural differences between the both treatment groups are often to be expected in cohort studies because the allocation to the treatment groups is not randomised. To be able to obtain an unbiased efficacy comparison between the treatment groups, the influence of the covariates on the efficacy criteria must be analysed and eliminated. This is one of the most fundamental differences in the evaluation concept between observational studies and controlled clinical trials.

In this cohort study the efficacy criterion "disappearance of all rheumatic symptoms at the termination of therapy" was used. This is a valid criterion which in general can be reliably ascertained out of medical records. In order to control the bias due to imbalances in observed covariates the logistic regression and the stratification in accordance to the propensity score were used. With the first method, the dependence of the treatment outcome on possible explanators is determined and the success change under an OE therapy compared to an NSAID therapy (odds ratio) using the same common values of all other covariates is estimated. This revealed an adjusted estimate of 1.5, meaning that with similar distributed covariates in both groups, a 50 % larger success odds in the OE rather than in the NSAID group is to be expected. The

difference is statistically highly significant. An analysis of the diagnosis groups shows that in joint diseases and spinal diseases on the whole a lower success rate than in soft tissue diseases can be expected, but that in all diagnosis groups the success rate with OE is larger than with NSAID. There are therefore no interactions between the therapy group and the diagnosis group. It is interesting that in patients who received a pre-treatment, a 50 % reduced success chance was to be expected. This supports the theory that, out of the pre-treated patients, in the main those patients come again for treatment who had little or no success with the pre-treatment and where in general the success rate is smaller. As patients with a pre-treatment were more often treated with OE, this explains the fact that the crude estimated success odds ratio for OE versus NSAID increased from 1.3 to 1.5 after controlling for differences with respect to relevant characteristics.

The second method used to balance the distribution of the covariates was the stratification of the patients according to the propensity score, to estimate the treatment success odds ratio and to summarise the estimates to a common odds ratio (in case of strata homogeneity). By definition, patients with similar propensity scores also have similar distributed covariates. Therefore, the values of the propensity scores can be used to define homogeneous strata (sub- groups) within the cohort. Because within these strata the efficacy of different treatments can be directly compared (the comparison is now no longer biased through different covariate patterns) we obtain an undistorted estimate of the relative efficacy of OE, if within every stratum, the odds ratio is calculated and summarised with a suitable procedure (Mantel-Haenszel procedure). It is demonstrated in table 7 that the stratification according to the propensity score really leads to a homogeneous distribution of the covariates between the treatment groups and in which for different strata of the propensity scores the frequency of pre-treated patients, patients without concomitant medication, and patients with additional analgesic usage are listed for both therapy groups.

Within one stratum of the propensity score practically no differences exist between the both treatment groups. Mind you, there are considerable (in accordance with the definition of the propensity score) differences between the strata. So patients with a propensity score of less than 40 % were barely pre-treated, but 80 % received a concomitant medication and 37 % additional analgesics. Patients with a propensity score of more than 80 % were in 60 % of the cases pre-treated, in less than 50 % received a concomitant medication and barely additional analgesics. In spite of these differences, the odds ratio for treatment success for OE is in all strata larger than 1. The differences between the strata are not significant, that means there are no significant interactions between the covariates and the treatment. The odds ratios of the strata can therefore be combined over all strata, the result being an adjusted mean (success) odds ratio for OE of 1.5 with a 95 % confidence interval of 1.161 to 1.840. At the stratification in accordance to the propensity score, the result is similar to that obtained by the means of logistic regression. This shows that the result, having a 50 % larger success odds with OE than with NSAID, does not depend on a special type of adjustment, but is obtained with various adjustment procedures. The result is of high plausibility. Of special importance is also that the comparison is based on the usual recommended doses for OE and NSAID regarding the investigated indications. Here the average daily doses of NSAID were 130 mg for diclofenac, 27 mg for piroxicam, and 1220 mg for ibuprofen.

The safety of the investigated enzyme combination preparation was evaluated as being without difficulties. This is valid in particular in the comparison to NSAID which were investigated parallel and showed – when prescribed in the effective doses – in the type, severity and frequency of the reported side effects the numerously described tolerability problems (18–20). An increased risk of gastropathy is present in the main in the elderly, patients with an anamnesis of gastric ulcers and patients who received a concomitant steroid therapy (21). Endoscopic investigations showed that approx. 30 % of the patients who took NSAID as a long term therapy develop a gastroduodenal ulcer. In the existing study nearly every third patient of the NSAID group reported gastrointestinal adverse events. In approx. half of these patients with gastrointestinal adverse events, a cost intensive gastro-protective medicinal therapy was applied. Here, the superiority of the enzyme therapy was shown to be evaluated clinically relevant, because in only about 4 % of the patients gastrointestinal symptoms were described. The only symptoms to be reported were stomach ache, diarrhoea and flatulence. These side effects are, out of the sight of the patient a far lower risk. Over and above they were easier to control and only in a very few cases there were additional therapeutic measures necessary.

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