Dissertation

PASI reduction and patient satisfaction after classical inpatient dithranol treatment

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used.

Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Date *Signature*

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ABBREVIATIONS

CID	Classical inpatient dithranol therapy
DLQI	Dermatology Life Quality Index
PASI	Psoriasis Area and Severity Index
PsoRA	Psoriasis Registry Austria

ABSTRACT

Dithranol, invented by Eugen Galevsky in 1916, is designated as one of the oldest, safest and most effective topical antipsoriatic treatments. Though, the well-known dithranol irritation in lesional and perilesional skin, which is tightly linked to its efficiency, represents a substantial cut-back. However, studies on dithranol's therapeutic efficacy according to a modern standard for scoring the extension of the disease such as the Psoriasis Area and Severity Index (PASI) reduction rates and patient perspectives on it have been scarce. Therefore, the recommendations with regard to topical dithranol treatment differ among various national guidelines. The aims of this thesis were thus as follows:

- The first aim of the thesis was to show the PASI reduction after a classical inpatient dithranol therapy (CID) by a retrospective analysis of data reported to the Psoriasis Registry Austria (PsoRA) (http://www.psoriasisregistry.at).
- The second aim was to provide information on the patient perspectives in terms of satisfaction, efficacy, adverse effects and recurrence-free interval after CID by using a telephone interview survey in a subset of these patients.

In total, data from 110 patients [75 men (68.2%) and 35 women (31.8%)] treated with CID had been reported to the PsoRA and were analyzed retrospectively for this thesis. The results of this thesis showed that CID is a highly effective and safe antipsoriatic treatment option which led in over 82.7% of the patients to a ≥75% reduction in PASI (PASI75) after treatment initiation within a median time of 14 days. The responses in the interview revealed that 77.2 % (44 out of 57) of the patients assessed CID as an effective antipsoriatic treatment option tied to an overall satisfaction in 61.7%, i.e. 37 out of 60 interviewed patients. Conversely, 56.9% (33 out of 58) of patients assessed CID as time consuming and 19.7% (12 out of 61) assessed its irritation as substantial or maximal. The median recurrence free interval after CID was stated with 4 (95% confidence interval, i.e., 3-9) months.

In summary, classical inpatient dithranol provides in many cases a faster remission of psoriasis than any other topical and/or systemic treatment option currently available. Beside the well-known CID therapy limitations (e.g. time consuming and CID irritation) patients assess CID as an effective antipsoriatic treatment option which provides satisfaction to a high portion of patients.

1 ZUSAMMENFASSUNG

Dithranol, eingeführt durch Eugen Galevsky 1916, zählt zu den ältesten, sichersten und effektivsten antipsoriatischen Lokaltherapien. Jedoch stellt die bekannte Irritation durch Dithranol von läsionaler und periläsionaler Haut, welche eng mit dessen Effektivität verbunden ist, eine wesentliche Einschränkung dar. Studien über die therapeutische Effektivität von Dithranol gemessen anhand von zeitgemäßen standardisierten Beurteilungsmethoden, wie dem „Psoriasis Area and Severity Index“ (PASI) und Ergebnisse zur Patientensichtweise liegen kaum vor. Aus diesem Grunde wird der Stellenwert einer topischen Dithranoltherapie in den verschiedenen nationalen Therapierichtlinien unterschiedlich beurteilt.

- Das erste Ziel dieser Doktorarbeit war es, die therapeutische Effizienz anhand der PASI-Reduktion nach einer klassischen stationären Dithranol-Therapie (CID) durch eine retrospektive Analyse von Daten des Psoriasis Registry Austria (PsoRA) (http://www.psoriasisregistry.at) zu zeigen.

- Das zweite Ziel lag darin, Informationen über die Patientenperspektiven bezüglich Zufriedenheit, Effektivität, Nebenwirkungen und dem rezidivfreien Intervall nach CID mittels einer Telefoninterview- Umfrage darzulegen.

Insgesamt wurden die Daten von 110 Patienten [75 Männern (68,2%) und 35 Frauen (31,8%)], welche mit CID behandelt und an das PsoRA berichtet worden waren, retrospektiv für diese Dissertation analysiert. Die Ergebnisse zeigten, dass CID eine hoch effektive und sichere antipsoriatische Therapieoption ist, welche bei 82,7% der Patienten zu einer ≥75% Reduktion des PASI (PASI75) im Median bereits 14 Tage nach dem Therapiebeginn führte. Die Antworten der Umfrage zeigten auch, dass 77,2 %, d.h. 44 von 57 der befragten Patienten CID als effektive antipsoriatische Therapie beurteilten mit der 61,7% (37 von 60) der Patienten insgesamt zufrieden waren. Hingegen empfanden 56,9% (33 von 58) der Patienten CID als zeitaufwendig und 19,7% (12 von 61) beurteilten die damit einhergehende lokale Irritation als beträchtlich oder maximal ausgeprägt. Das mediane erscheinungsfreie Intervall nach CID wurde von den Patienten mit 4 Monaten (95%-Konfidenzintervall: 3-9) angegeben.

Zusammenfasend führt CID in vielen Fällen zu einer schnelleren Remission der Psoriasis als alle anderen derzeit verfügbaren topischen und/oder systemischen Therapieoptionen. Trotz der hinlänglich bekannten Therapieeinschränkungen von CID (wie Zeitaufwand und lokale Irritation) beurteilen die Patienten CID als eine effektive antipsoriatische Therapieoption, welche bei einem großen Teil der Patienten zu Therapiezufriedenheit führt.

2 INTRODUCTION

2.1 Psoriasis

2.1.1 Definition and classification

Psoriasis is a polygenetic, chronic inflammatory and multi-systemic disease, depicted by cutaneous lesions with varying degrees of erythema, scaling, thickening and infiltration of the skin and body surface area affected. With a prevalence of more than 2 % in the Western World psoriasis represents one of the most common inflammatory diseases (1-3).

The disease can be classified in regard to its different manifestations (i.e., guttate, plaque, inverse type), its acuteness of lesions and disease course (i.e. acute exanthematic and a chronic plaque type) (4). In addition, an older classification subdivides psoriasis by course and prognosis (1). Type 1 psoriasis is associated with an initial disease manifestation before the age of 40 years, a family history positive for psoriasis, HLA-Cw6 status and a more severe disease course. Type 2 psoriasis (with delayed disease onset) initially occurs after the age of 40 years, frequently with a negative family history for psoriasis and without a strong association with genetic markers. Additionally, type 2 psoriasis is linked to a less severe disease course.

2.1.2 Genetics, etiology and pathogenesis

The etiology of psoriasis is multifactorial. A genetic constitution as shown by twin and family studies and genome-wide association studies (5, 6) as well as environmental factors such as infections, certain drugs and smoking are essential and interacting elements in the pathogenesis of the disease. Genome-wide association studies revealed multiple susceptibility loci (PSORS1-9) for psoriasis. One of these, PSORS1, located on chromosome 6p21 was linked to the disease in almost every study. This region (chromosome 6) inter alia carries the genes for HLA-C (associated variant, HLA-Cw6) which encodes a class I MHC protein. Polymorphic coding-sequence variants of HLA Cw6 features the strongest association with psoriasis, especially with the early onset form (type 1). Heterozygote carriers of the HLA-CW6 allele have a 9-fold- and homozygote carrier an up to 23-fold increased risk to develop psoriasis. Recent studies have indicated a link to genetic variations influencing pro-inflammatory cytokine pathways (e.g. TNF-α, IL-23) in psoriasis. However, a psoriasis-specific mutation has not (yet) been identified until now and the mode of inheritance appears to be rather complex. Therefore, genetic variants in susceptibility loci may influence the downstream of multiple genes (1, 3).

Histologically, psoriatic lesions show a severe inflammatory infiltrate and epidermal hyperproliferation as well as an abnormal keratinocyte differentiation. The inflammation appears to be driven by both the innate and adaptive immunity. The primary nature and first link in the chain, in particular in which part of the immunity the inflammatory cascade starts is unclear. However, under the influence of increased levels of pro-inflammatory cytokines (i.e. IL-12, IL-23, TNF-α) certain T-cell subpopulations (i.e. Th1 cells and Th17 cells) are expanding that in turn secrete pro-inflammatory cytokines (i.e. TNF-α, IL-17 and IL-22). Consecutively, cells like endothelial cells, fibroblasts and keratinocytes in turn boost the immune response through expression of surface molecules and/or release of mediators. Attracted by the inflammatory process neutrophilic granulocytes migrate in the tissue and form the typical sterile epidermal micro abscesses (1).

2.1.3 Clinical manifestation

Classical manifestations of psoriasis include the following types:

- chronic plaque
- guttate
- intertriginous
- inverse

More rare variants and potential separate diseases entities are the following types:

- pustular (generalized and localized with its palmoplantar variant)
- acrodermatitis continua suppurativa Hallopeau

Independent from its primary clinical manifestation psoriasis can lead to an erythrodermic skin condition which is marked by a reduced health state (e.g. fever, exsiccosis, high energy consumption) with generalized fiery red skin.

In addition to psoriatic skin manifestations nail involvement can be observed in up to 50% of psoriasis patients (7).

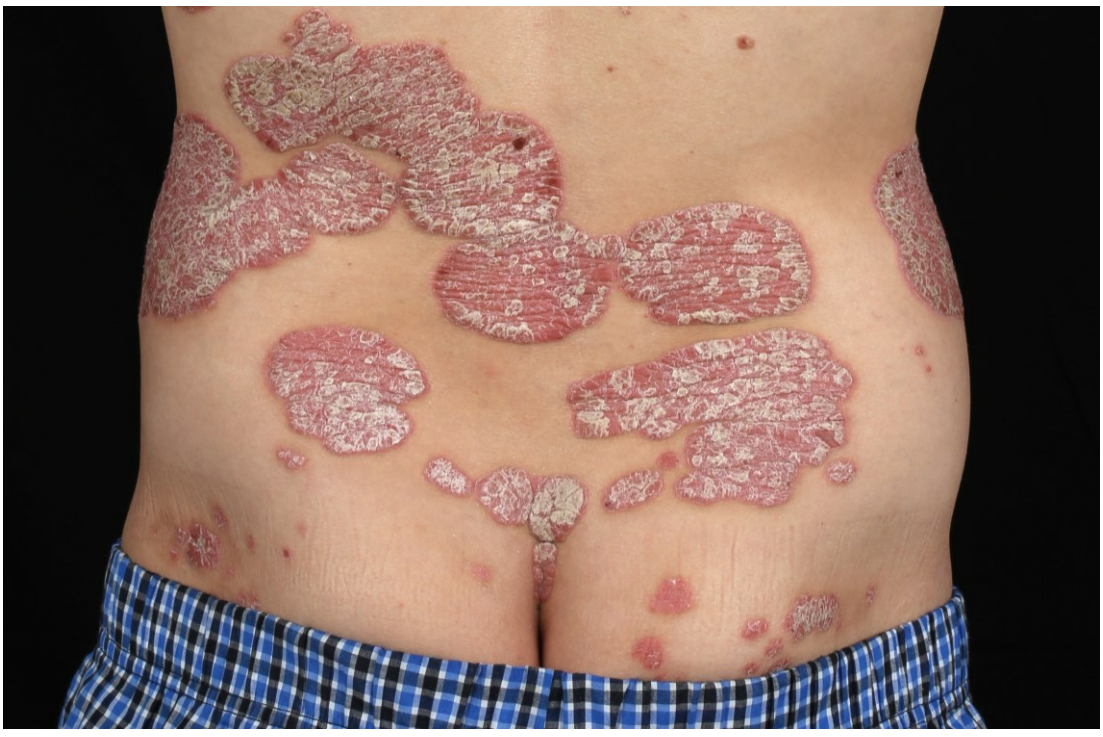
Typical clinical signs of nail psoriasis are:

- oil-drop discoloration
- pitting
- leukonychia
- crumbling of the nail plate
- subungual hyperkeratosis

2.1.3.1 Chronic plaque psoriasis

Chronic plaque psoriasis is the most frequent clinical manifestation of psoriasis vulgaris. The plaque type is characterized by single or multiple (potentially confluent), erythemato-squamous plaques distributed mainly located on the extensor sites of the extremities (e.g. knees/shines, and elbows) or sacral area and buttocks. These lesions may hold on stationary for years or progress to affect the entire body surface. The progress may occur due to environmental and/or endogenous factors (e.g. infections, certain medications, and/or stress) which are well known in triggering psoriasis (1).

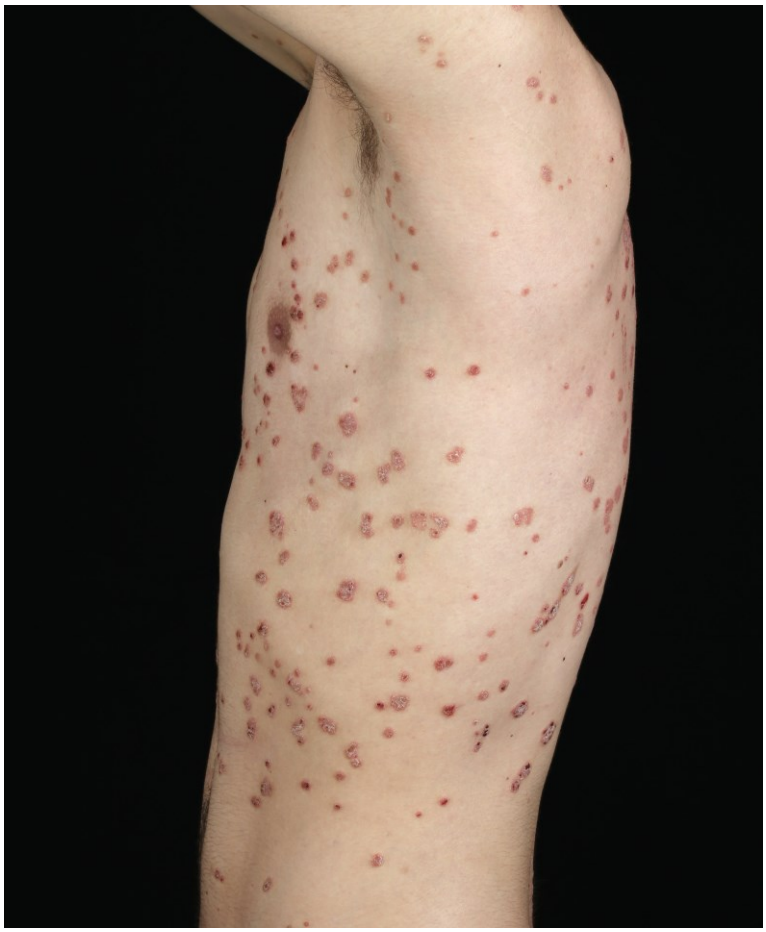
Picture 1) Plaque psoriasis in the sacral area
Image source:
Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.3.2 Guttate psoriasis

The guttate type of psoriasis is marked by the appearance of drop-shaped erythemato-squamous lesions with a diameter up to 1.5 cm which can affect the entire skin surface. The guttate type is often the first clinical manifestation of psoriasis and mainly occurs in childhood or adolescence in response to an infection (especially of streptococcal origin). A shift from the guttate type to the plaque type may occur (1).

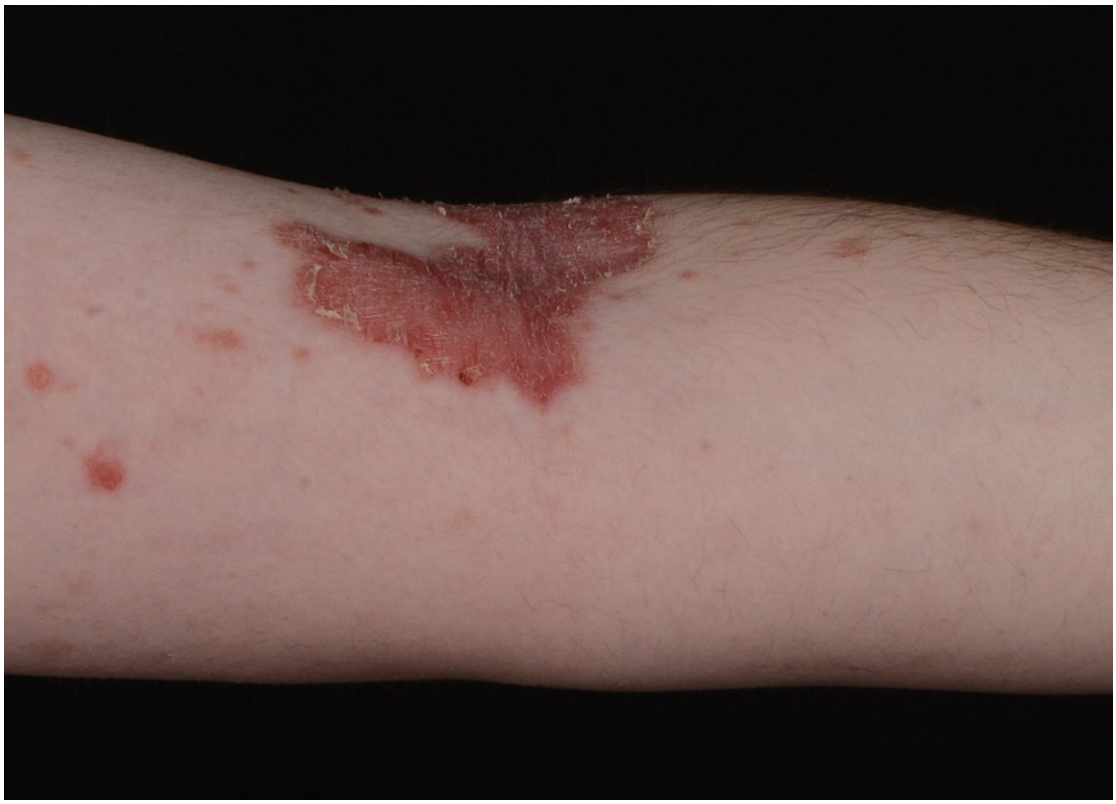
Picture 2) Guttate psoriasis on the trunk
Image source:
Psoriasis Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.3.3 Psoriasis inversa

Psoriasis inversa is characterized by the occurrence of psoriasis lesions exclusively on the flexural surfaces of the major joints (inverse to the plaque type (predilection sides: extensor sides of the joints) (1).

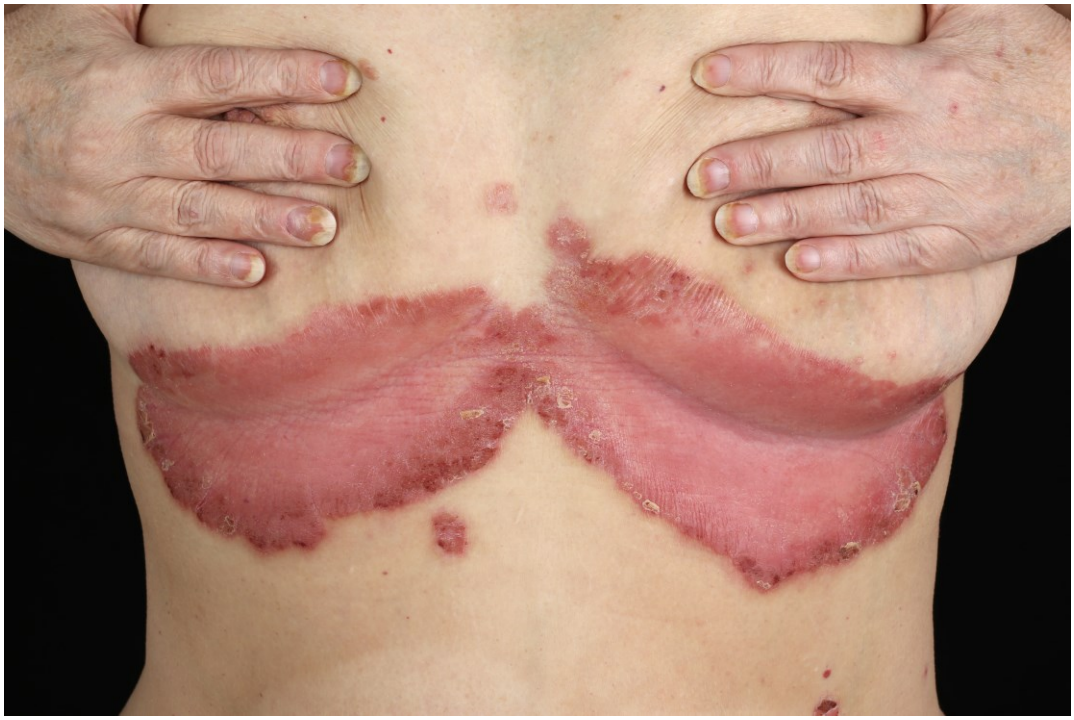
Picture 3) Psoriais inversa in the cubital fossa
Image source:
Picture archive of the Department of Dermatology, Medical University of Graz



2.1.3.4 Intertriginous Psoriasis

Intertriginous psoriasis is a rare manifestation which mainly affects body sites with skin folds (e.g. submammary region, axillae, inguinal and anal region) (1).

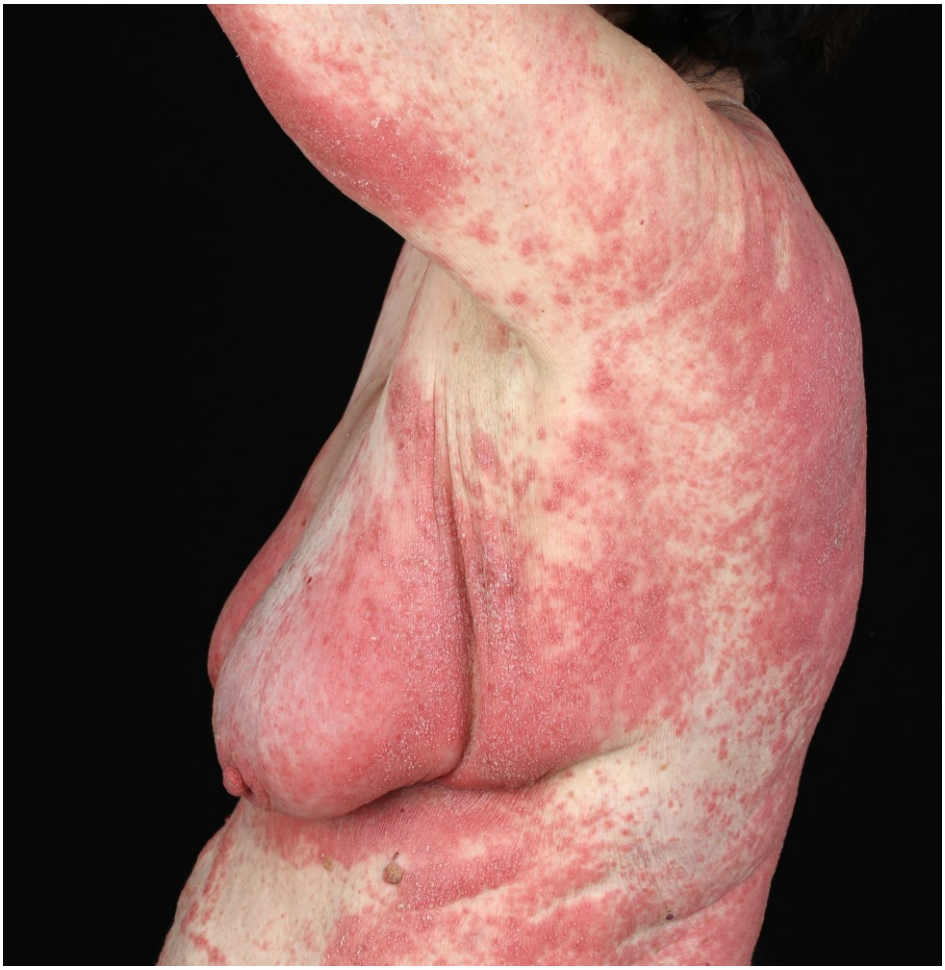
Picture 3) Intertriginous Psoriasis in the submammary folds
Image source:
Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.3.5 Pustular psoriasis

Several clinical variants of Pustular psoriasis are described. The clinical presentation of generalized pustular psoriasis is marked by an occurrence of multiple disseminated pustules and a potential reduced general health state (e.g. fever, feeling of being unwell) and dermopathic lymphadenopathy.
Pustules may also occur in other clinical variants of psoriasis (e.g. chronic stationary plaque psoriasis) associated to an acute exacerbation of the disease. In that case, its occurrence is designated as psoriasis cum pustulatione (1).

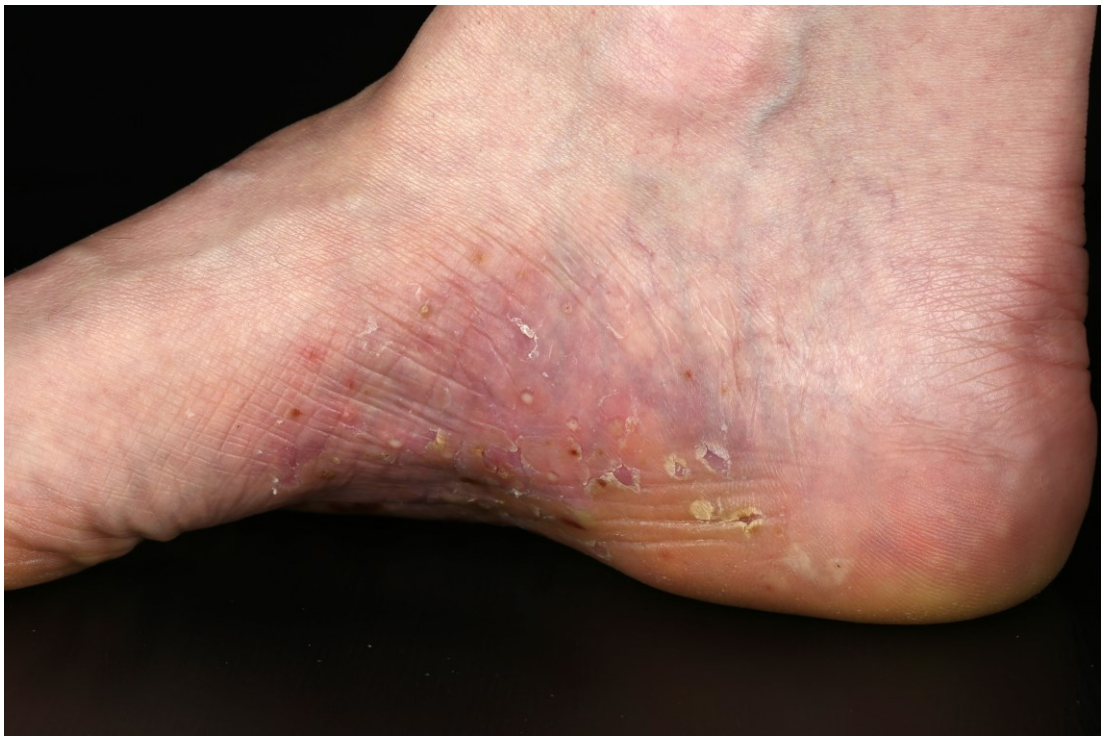
Picture 4) Psoriasis pustulosa generalisata
Image source:
Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.3.6 Palmoplantar pustulosis

Today Palmoplantar pustulosis is separated from the classic variants of psoriasis and is included in the group of acropustular forms of the disease, in which multiple pustules emerge on the soles of the feet and/ or the palms of the hands (1).

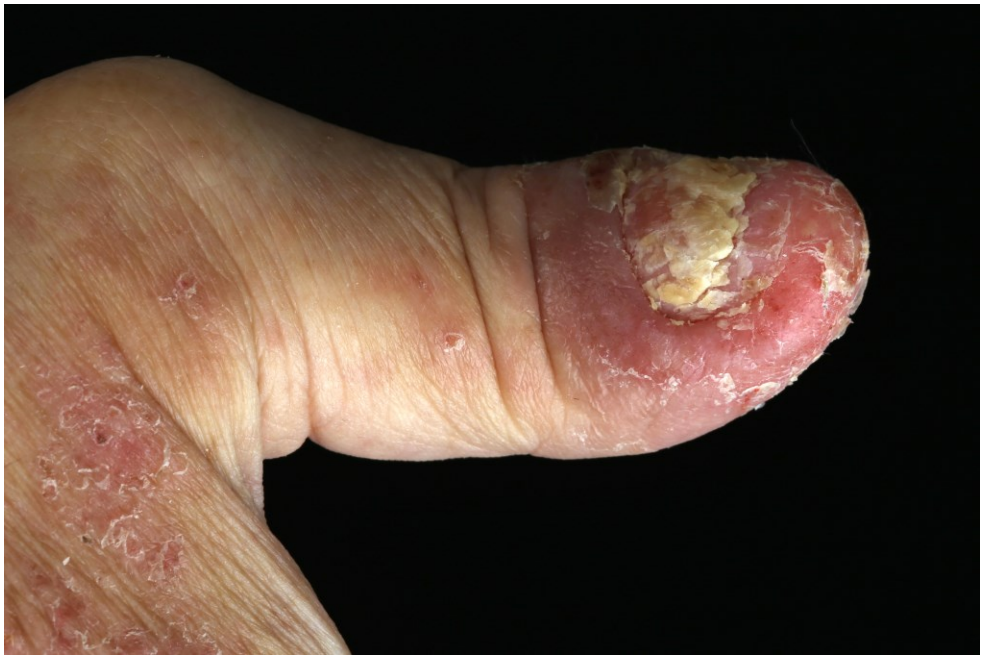
Picture 5) Plantar pustulosis
Image source:
Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.3.7 Acrodermatitis continua suppurativa (Hallopeau)

Acrodermatitis continua suppurativa (Hallopeau) is also included in the group of acropustular forms of psoriasis. This very rare diseases variant is marked by severe inflammation in acral regions which leads to lakes of pustules, loss of the nails and potential destruction of the distal phalanges (1).

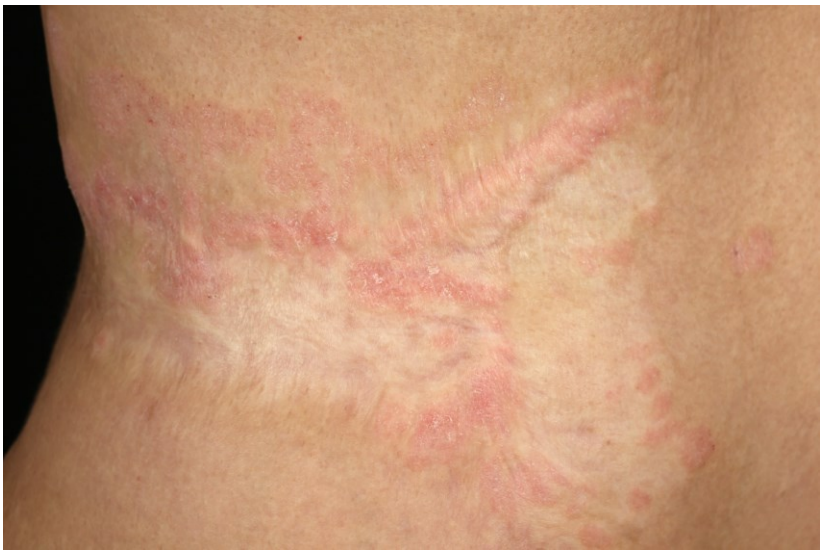
Picture 6) Acrodermatitis continua suppurativa on the right thumb
Image source:
Picture archive of the Department of Dermatology, State Hospital Klagenfurt



2.1.4 Koebner phenomenon

In 1872 Heinrich Koebner (1838-1904) firstly presented at conference the phenomenon, whereby psoriatic lesions emerge in turn of a trauma to unaffected skin of psoriasis patients (8, 9). The pathophysiologic mechanism of the "Koebner phenomenon" remains still unclear. Though, immunological and vascular mechanisms are mainly discussed. Baker et al. observed an increased ratio of CD_4/CD_8 cells in unaffected skin of psoriasis patients. It was suggested that an increase of CD_4 cells in the skin may be associated with a higher risk to develop a "Koebner phenomenon", whilst CD_8 cells might have a protective character (10). Telner and Fekete showed in 1961 significant micro vascular alterations resulting from scars in psoriatic patients compared to non-psoriatic individuals (11). A further hint for the vascular involvement might be a reduced incidence rate of artificial induced "Koebner phenomena" achieved by a pre-treatment with vasoconstrictors like epinephrine (12). In addition to that an increased mast cell rate in fresh scars of psoriasis patients might be a further factor (13). Also genetic factors may play a role in Koebner phenomenon. In that line Guedjonsson et al. showed an association between an increased incidence rate of Koebner phenomenon and HLA-Cw6 (14).

Traumas which may induce a Koebner phenomenon are various and include: injuries (e.g. incision- ore bite wounds), surgical treatment, injections, rubbing and compressions effects (e.g. resulting from compression stockings or trouser buttons), piercings, tattoos and every type of dermatitis regardless of its etiology (e.g. type IV hypersensitivity to nickel, erythema chronicum migrans) (15-17).



Picture 7)
"Koebner phenomenon"
in a scare.

Image source:
Picture archive of the
Department of Dermatology,
State Hospital Klagenfurt

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2.1.5 Measurement of psoriasis disease severity by "Psoriasis Area and Severity Score Index (PASI)"

The PASI was firstly described in a study assessing the therapeutic efficiency of an oral retionoid in psoriasis patients published by T. Fredriksson and U. Pettersson in 1978 (18). Fredriksson et al. established this score in the above mentioned study by determining it at four different times (week 2, 4, 6 and 8) in 27 patients (18). Over time, PASI became the gold standard (in studies and daily clinical use) for assessing severity and therapy outcome in psoriasis of chronic plaque, guttate, intertriginous and inverse type (1, 19, 20).

The PASI assesses the severity of psoriasis by considering the skin surface condition and affected body surface area (BSA).

The surface condition is assessed by the determination of three cardinal symptoms (erythema, induration and desquamation) on a five point ordinal scale (Table 1).

Table 1) PASI single scores for the three cardinal symptoms

Erythema (redness)				
0= none	1= mild	2= moderate	3= severe	4= very severe
Induration (thickness)				

0= none	1= mild	2= moderate	3= severe	4= very severe
Desquamation (scaling)				
0= none	1= mild	2= moderate	3= severe	4= very severe

The BSA is assessed by subdividing the body surface into four compartments:

I) Head
II) Trunk
III) Upper extremities
IV) Lower extremities

According to this scheme the head represents 10%, the trunk 30%, the upper extremities 20% and the lower extremities 40% of the BSA.

The affected area in those four compartments is estimated and counted with a numerical value:

1=<10%

2= 10-<30%

3= 30-50%

4= 50-70%

5= 70-90%

6= 90-100%

The BSA is calculated in the following way:

$$BSA = [(0.1 x A_h)+(0.2 x A_u)+(0.3 x A_t)+(0.4 x A_l)]$$

A = numeric value of the affected area

H = head

U = upper extremities

T = trunk

L = lower extremities

As already described, beside the relative amount of the affected BSA the PASI includes the assessment outcome of the three cardinal symptoms (erythema, induration and desquamation) determined on a five point ordinal scale on the head, trunk, upper extremities and lower extremities.

$$PASI = 0.1(E_h+I_h+D_h)A_h+0.3(E_t+I_t+D_t)A_t+$$

$$0.2(E_u+I_u+D_u)\ A_u+0.4\ (E_l+I_l+D_l)\ A_l$$

A = numeric value for the single score of the specific body site

E = erythema (redness)

I = induration (thickness)

D = desquamation (scaling)

h = head

u = upper extremities

t = trunk

l = lower extremities

The scale which results from this formula reaches from 0 to 72. According to the German S3 guidelines a disease manifestation with PASI <10 is considered as mild and PASI>10 as moderate-to-severe psoriasis (1).

2.1.6 Psoriasis: More than a skin disease

Up to 70% of all psoriasis patients develop a sero-negative inflammatory arthritis which potentially involves peripheral joints, entheses and the spine (21). An older classification, firstly described by Moll and Wright in 1973, subdivides psoriasis arthritis in five subtypes (22), i.e. mono- or oligoarthritis, polyarthritis, distal interphalangeal predominant disease, spondylitis and/or sacroiliitis and mutilating arthritis (22). A updated classification for diagnosing psoriasis arthritis (CASPAR) (23) considers the following criteria: the evidence of cutaneous psoriasis (current, personal history or family history of psoriasis), psoriatic nail dystrophy (e.g., onycholysis, pitting and hyperkeratosis), a negative rheuma factor, dactylitis (history of or current swelling of an entire digit) and radiological evidence of juxta-articular new bone formation (23). However, the clinical manifestation of psoriatic arthritis is rather heterogeneous complicating the development of simple and robust classification criteria. Regarding the high risk of the development of arthritis in the course of the disease early recognition and subsequent adequate treatment is necessary to prevent potential permanent joint damage and disability.

Psoriasis is linked to a higher rate of comorbidities compared to the general population (24). The risk for the development of specific comorbidities in the course of psoriasis is increased in patients with a more severe skin manifestation (24). A variety of specific comorbidities such as chronic inflammatory diseases (i.e. rheumatoid arthritis, chronic inflammatory bowel diseases), metabolic syndrome (diabetes, obesity, dyslipidemia and arterial hypertension) and cardiovascular diseases (i.e. peripheral vascular diseases, heart attack and stroke) (1, 24) have been linked to psoriasis in the past years. In addition, there is increasing evidence for a link between psychiatric disorders (i.e. affective disorders and depression) and psoriasis (25). Finally, regarding the increased rate of comorbidities, a study indicates a reduced life expectancy in severe psoriasis patients by more than four years (26).

Many investigations on psoriasis-associated comorbidities have been gained from observational (case-control based) studies, although these data do not allow the identification of the cause-and-effect relationship.

Irrespectively, prospective studies, investigating temporal sequences where the presence of psoriasis may result in an increased incidence rate of certain comorbidities (or vice versa) are needed. However, the increased comorbidity rate of psoriasis patients compared to a normal population suggests a multi-systemic impact of the chronic inflammatory diseases psoriasis.

2.1.7 Quality of life

Due to stigmatizing skin lesions and discrimination, retrenchments in daily life, comorbidities and therapy costs psoriasis strongly impacts the quality of the patients' life. This impact on quality of life is documented in various studies (27-31). For example, nearly half of the patients with psoriasis feel physically unattractive or sexually undesirable. In addition, psoriasis patients have higher divorce rates relative to that of other chronic illnesses. Anxiety and depression exists in up to 30% of patients regardless of the severity of their disease. Indeed, over 50% of patients classified having moderate-to-severe disease report depression (32). Moreover one study comparing quality of life scales of different diseases suggests that quality of life in psoriasis patients is even more impaired than in patients with diabetes, coronary heart disease and cancer (1).

Regarding the significant increased risk of physical and psychological impairments in psoriasis patients, the development and use of standardized assessment tools that give measure of quality of life during treatment seems essential. The most frequently used and guideline- recommended tool is the Dermatology Life Quality Index (DLQI). It has been first described in 1994 by Finlay et al. (33) and is assessed with a validated questionnaire composed of 10 items (regarding itch, self-consciousness, interference in daily activities, clothing style, social activities, sport, work, partnerships, sexual difficulties, treatment associated problems) measuring how much the skin disease has affected the life over the last week. The close inverse relationship between psoriasis extension measured by PASI and quality of life measured by DLQI has been demonstrated in several studies. The results of these studies showed a PASI reduction-dependent correlation of DLQI outcomes, with significant differences comparing PASI50, 50-70, 75 reduction rates as clinical endpoint (34-36). Thus, the optimal monitoring of psoriasis patients includes frequent DLQI determination.

2.1.8 Therapy concepts

The etiology of psoriasis and its pathomechanisms are not fully understood and curative treatment is at present not available. Hence current psoriasis treatment concepts broadly focus on managing the symptoms with local or systemic therapy approaches according to the disease activity. Due to the chronic course of the disease, in many cases a lifelong lasting immunomodulatory and/or antiproliferative treatment accompanied with potential risks and side effects is required to provide relief.

Figure 1) Psoriasis therapy overview adapted from Nast et al. (1)

TOPICAL THERAPY
Calcineurin inhibitors
Dithranol
Corticosteroids
Laser therapy
Tazaroten
Tar
Vitamin D3 analogues

SYSTEMIC THERAPY		
Conventional	Biologics	*New small molecules
Methorexat	Adalimumab	Apremilast
Phototherapy (UVB, Balneo photo, PUVA)	Etanercept	
Retinoids	Infliximab	
Fumaric acid esters	Ustekinumab	
Cyclosporine	*Secukinumab, Ixekizumab	

* Already approved, not jet included in the guideline

2.2 Dithranol

2.2.1 History

In 1864, D.S. Kemp reported about a substance known as chrysarobin available from Bombay, which was used for the therapy of persistent skin diseases particularly in Europe. The irritative side effect and the increasing import restrictions of the raw materials of chrysarobin during the naval blockade of World War I led to the development of a synthetic chrysarobin derivate named dithranol (an anthracene derivate known in the US as anthralin; in Germany as cignolin).

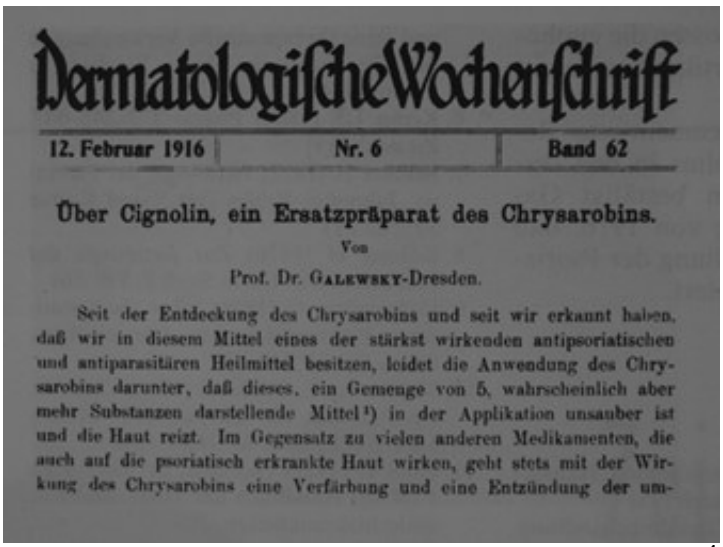
It was introduced as a variable therapeutic agent by Eugen Galevsky a dermatologist in Dresden, Saxony. Eugen Galevsky published his experience with the drug in 1916, where he concluded that the substance improves the treatment of psoriasis essentially. Following these results, the company Farbenfabrik Bayer in Leverkusen finally obtained a patent for the synthesis of 1.8 dihydroxyanthrone in 1916.
Since its market launch, dithranol was used by dermatologists as a gold standard agent in the treatment of psoriasis over decades and is still used (37, 38).

Picture 8)
Eugen Galevsky (1864-1935)

Image source:
Scholz A., Dtsch Arztebl 2012;

Picture 9)
Manuscript: „Über Cignolin, ein Ersatzpräparat des Chyrsarobins”

Image source:
Scholz A., Der Hautarzt; 1991;



Dermatologische Wochenschrift

12. Februar 1916 | Nr. 6 | Band 62

Über Cignolin, ein Ersatzpräparat des Chrysarobins.

Von

Prof. Dr. Galewsky-Dresden.

Seit der Entdeckung des Chrysarobins und seit wir erkannt haben, daß wir in diesem Mittel eines der stärkst wirkenden antipsoriatischen und antiparasitären Heilmittel besitzen, leidet die Anwendung des Chrysarobins darunter, daß dieses, ein Gemenge von 5, wahrscheinlich aber mehr Substanzen darstellende Mittel[1]) in der Applikation unsauber ist und die Haut reizt. Im Gegensatz zu vielen anderen Medikamenten, die auch auf die psoriatisch erkrankte Haut wirken, geht stets mit der Wirkung des Chrysarobins eine Verfärbung und eine Entzündung der um-

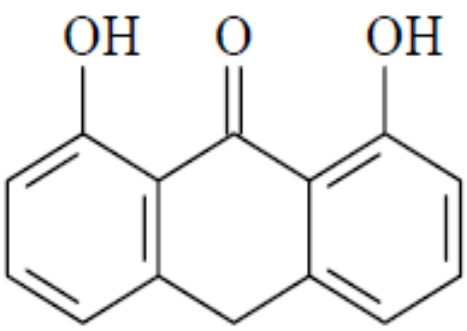
2.2.2 Structure and mechanism

Dithranol (1,8-dihydroxy-9(10H)-anthracenone, Figure 2), the synthesized derivate of chrysarobin inhibits under physiological conditions the proliferation of keratinocytes (39). In vivo dithranol's oxidation leads to 9-anthron-10yl radical and superoxide and hydroxyl radicals (39). The 9-anthron-10yl radical is suggested to be a key intermediate (39). The following oxidation and polymerization is sought to result in the formation of secondary anthralin brown radicals. These secondary anthralin brown radicals show an inert character.

Free radicals resulting from dithranol's oxidation, especially 9-anthron-10yl radical, are suggested to destroy the DNA of cells and inactivate regulatory enzymes (e.g. proliferative and pro-inflammatory enzymes). The induction of pro inflammatory mediators and a consecutive adapted inflammatory gene expression caused by unstable oxygen intermediates have been discussed (40). The activation of a key transcription factor of inflammation and immune response (nuclear factor-ϰB) might be involved in the therapeutic mechanism of dithranol (41). Finally, the inactivation of epidermal phosphofructokinase and glucose-6-Phoshate dehydrogenase through malonaldehyde a product of lipid peroxidation due to oxidative stress has been observed (42).

Figure 2)

Dithranol (1.8-Dihydroxy-9(10H)-anthracenone)



2.2.3 Mode of action in psoriasis

Despite it's over 100 year's successful history, the mechanisms of dithranol in clearing psoriatic skin lesions remain not well understood (40). Since dithranol triggers an inflammatory reaction, one would expect as a result the aggravation of psoriatic skin changes in the sense of a "Köbner phenomenon" rather than clearance of skin lesions.

However, the basic pathogenetic concept of psoriasis refers to an activation of T-lymphocytes which in turn may result in keratinocyte proliferation. In that inflammatory cycle lymphocytes as well as keratinocytes again release factors (e.g. TNF-α, Interleukins and growth factors) which boost inflammation. In addition an influx of inflammatory cells (e.g. leukocytes, monocytes and neutrophils) and an up-regulated expression of intracellular as well as vascular cell adhesion molecules can be observed in the pathophysiology of psoriasis. Dithranol is suggested to interfere in nearly all of these pathogentic steps.

Dithranol shows strong anti-proliferative properties on keratinocytes, related to down regulation of the epidermal growth factor (EGF) receptor, decreased EGF receptor binding and decreased expression of keratinocyte transforming growth factor-α on epidermal cells (43-46). Furthermore, the inhibition of neutrophilic granulocytes and monocytes as well as the migration of leukocytes and proliferation of lymphocytes has been observed (47, 48).

Dithranol also leads to significant inhibition of the production and release of pro-inflammatory cytokines (IL-6, IL-8 and TNF-α) from monocytes which might be a result of a DNA inhibiting effect (48).

Finally the release of free radicals due to the oxidation of dithranol leads to an inhibition of DNA synthesis, cellular enzymes, and/or mitochondria function which might be essential for the antipsoriatic effect of the drug (49).

Interestingly, reports indicate that dithranol may also cause clearing of untreated psoriatic lesions at distant body sites. This clearing of untreated plaques is assumed

as an indirect effect of circulating factors or certain cells from treated areas (50). A systemic impact of dithranol is not expected due to the barely detectable amounts of the drug when topically applied (50).

2.2.4 Therapeutic dithranol regimes and ointments for psoriasis

According to the German S3 Guidelines for the treatment of psoriasis two different dithranol treatment regimens are recommended:

- short contact treatment
- classical therapy regime

In order of the therapy regime an easy to rinse off ointment base with a higher dithranol concentration (short contact treatment) or adhesive ointment base with a lower dithranol concentration (classical therapy regime) is commonly used (51).

Importantly, dithranol is very sensitive to oxidation. Therefore dithranol ointments have to contain anti-oxidants. For the chemical stabilization salicylic acid in a 0.5% concentration is a proven anti-oxidant in dithranol ointments, which in the 0.5% concentration, fells substantially below the therapeutic concentration (51). Complementary, to enhance the chemical stabilization of dithranol ointments ascorbic acid or butylated hydroxytoluene may be added. Due to the pronounced photo- and oxygen sensitivity dithranol ointments have to be stored in aluminum tubes (51).

2.2.4.1 Dithranol short contact therapy

The dithranol treatment in its short-contact form is applied to affected skin, at start with a low concentration (usually of 0.5-1%) of the drug. Within the first 10 days of treatment duration the cream is commonly rinsed off after 10 minutes. Depending on the degree of the skin irritation, the concentration of the drug (up to 2-3%) and the dwell time (up to 30 minutes) can be increased. The short contact therapy is preferable performed in an outpatient or day clinic setting (1).

Due to the short dwell time in the short contact therapy regime the ointment base should be easy to rinse off. Therefore the German Pharmaceutical Codex/ (Neues Rezeptur-Formularium [NRF]) provides a few easy to rinse off extemporaneous preparations (51).

Table 1) Example for a rinseable extemporaneous preparation (NRF 11.52.):

Rinseable dithranol ointment:	0.05%	0.1%	0.25%	0.5%	1%	2%
Dithranol:	0.5 g	0.1 g	0.25 g	0.5 g	1.0 g	2.0 g
Salicylic acid:	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
Rinsable oinmement base*:	100.0 g	100.0 g	100.0 g	100.0 g	100.0 g	100.0 g

*Rinsable ointment base (NRF S3.1):

Natriumdodecylsulfat: 50%: 10.0 g

Sorbitanmonostearat, Typ I: 20.0 g

White Vaseline: 20.0 g

2.2.4.2 Classical dithranol therapy

In its classic form of treatment the dithranol cream is applied to lesional skin starting with a very low concentration (0.1%) of the drug and is not (or if, after 24h) rinsed off. The dithranol concentration is increased depending on the degree of the skin irritation, usually every second day up to a concentration of 1%. The classical dithranol therapy is mainly performed in an inpatient care setting (1).

For the classical dithranol therapy lipophilic ointments are useful, because the active agent penetrates the epidermis more sufficient in a lipophilic than in a hydrophilic ointment (51). The rinsebility is in the classical regime secondary (51). To improve the permeability of the agent the adding of salicylic acid in therapeutic concentration to solve the scales from psoriasis plaques is recommended (51). A ready-to-use product is currently not available at the market though the German Pharmaceutical Codex/ (Neues Rezeptur-Formularium [NRF]) provides a few extemporaneous preparations (51).

Table 2) Example for an extemporaneous preparation for the classical dithranol therapy regime (NRF 11.53.):

Dithranol Vaseline:	0.05%	0.1%	0.25%	0.5%	1%	2%
Dithranol:	0.05 g	0.1 g	0.25 g	0.5 g	1.0 g	2.0 g
Salicylic acid:	2 g	2 g	2 g	2 g	2 g	2 g
High-viscosity paraffin:	2.0 g	2.0 g	2.0 g	2.0 g	2.0 g	2.0 g
White Vaseline	100.0 g	100.0 g	100.0 g	100.0 g	100.0 g	100.0 g

2.2.4.3 Further dithranol therapy regimes in psoriasis

Ingram regimen

This combination therapy is composed of a coal tar bath followed by a UV radiation (broad or narrowband UVB) and topical dithranol treatment (short contact or classical regime) (40, 52-54). According to a study by Vella Briffa et al. the Ingram regime seems to be highly effective and leads to a complete remission of psoriasis lesions in 82% within 20 days (55). Due to the carcinogenic potential of coal tar and the time consuming as well as inconvenient procedure of the Ingram regimen especially by considering the nowadays available treatment options, it can't be longer recommended as first line approach.

Dithranol minute entire skin treatment

According to a recent review (40), dithranol minute entire skin treatment (56, 57) was introduced to optimize the cosmetic result as well as the efficacy of the dithranol short contact regime. Hereby dithranol is applied to lesional and perilesional skin with a 10 minute dwell time. The dithranol concentration is individually administered depending on the irritative side effect. This regime was proposed to avoid the brown spotty pigmentation after dithranol treatment. Though, by considering this regime one does wonder if the prevention of the brown spotty pigmentation might not lead to area wide brown pigmentation. However, the dithranol minute entire skin treatment is not generally accepted since it is not compromised in the German (1), British (58) or American (20) guideline for the treatment of psoriasis.

2.2.5 Dithranol in warts and alopecia areata

2.2.5.1 Dithranol in warts

Due to the known antiproliferative effects on keratinocytes dithranol is also used in the treatment of warts. Initially to soften the tissue it is recommended to treat the hyperkeratosis with a high concentrated salicylic acid ointment (51). After the softening the dithranol ointment is applied twice daily on the warts for a few weeks (51).

Dithranol treatment in warts shows clearance rates up to 77% (51, 59, 60). Flindt-Hansen et al. studied in a randomized controlled trial the efficacy of a keratolytic- compared with that of a 2% dithranol ointment (59). After a two month period of treatment, their data showed superiority in the clearance rate of warts for the dithranol treatment arm (56 vs 26%) (59).

A ready-to-use product for the dithranol treatment in warts is not available, though extemporaneous preparations are provided in the German Pharmaceutical Codex/ (Neues Rezeptur-Formularium [NRF]) (51).

Table 3) Example for an extemporaneous preparation for a dithranol wart treatment (NRF 11.31.):

Dithranol wart ointment	
Dithranol:	1.0 g
Salicylic acid:	25.0 g
High-viscosity paraffin:	5.0 g
White Vaseline	100.0 g

2.2.5.2 Dithranol in alopecia areata

The therapeutic mechanisms of dithranol as well as the pathogenesis itself in alopecia areata remains still unclear (40). Though, it is suggest that certain proinflammatory cytokines (e.g. TNF-α) may play a major role in the pathogenesis (40). Addressing the molecular pathomechanismens and the therapeutic effect of dithranol in alopecia areata Tang et al. conducted a study in a mouse model (61). They observed decreased TNFα levels in the treated areas of responding mice. Conversely TNF-α levels of non-responders have not been influenced (61). Other cytokines (e.g. IL-18, IL-1Ra, IL-1a, IL-1b, IL-10 and IL-12) remained unchanged in the comparison of treated and untreated areas (61). In addition, TNF-α m-RNA was not traceable from the mouse skin, moreover TNF-α and IFN-Y m-RNA expression were decreased (61).

Both, the classical and short contact regime are recommended for the treatment of alopecia areata (40). Similar to the psoriasis therapy regimes concentrations from 0.1% up to 3% are used (40, 62). Higher concentrations (i.e. 1-3%) for the short contact and lower concentrations for the classical regime (e.g. 0.1-0.4%) are used. In the short contact regime the dithranol ointment is applied on the hairless areas once daily with a dwell time up to 30 minutes over a two week period (40, 62, 63). The dithranol concentration as well as the dwell time is increased depending on the irritative effect, whereby a mild erythema and pruritus is desired for the therapeutic effect. After reaching this state the treatment should be continued by keeping up the mild erythema and pruritus for 3-6 month (63).

Success rates with dithranol treatment in alopecia areata ranging from 25% up to 60% (64-67).

2.2.6 Further indications for dithranol treatment

According to a review by Shegal et al. a successful use of dithranol in the treatment of an inflammatory linear verrucosus epidermal nevus has been published (68, 69). In addition, low concentrated dithranol ointment seems to be effective in the treatment

of facial seborrheic dermatitis (70). However, especially in the latter condition extreme caution has to be taken due to the irritative effect of dithranol.

2.2.7 Safety

Dithranol is regarded the oldest and safest topical therapeutic of psoriasis, as evidenced by its missing systemic and long term local side effects (1). Though, the reversible irritant and browning effect of lesional and perilesional skin represents a major limitation of this therapy.

2.2.7.1 Irritant effect

The oxidation of dithranol generates oxygen radicals which induce an irritation marked by an itchy and burning erythema of the skin. Increased levels of prostaglandin E2 directly correlate with the occurrence of an early irritation (erythema) after dithranol treatment (40).

Though, this irritation of lesional and perilesional skin, is closely related to dithranols' efficacy (1, 71) and the severity of dithtranols' irritative response correlates well with its contact time and concentration. Therefore, dithranol treatment requires a very compliant patient as well as supervision and the dermatologist´s attention. According dithranol treatment is mainly performed in day care or inpatient settings.

In order to reduce the irritant side effect of dithranol the use of local steroids as a pre-, concomitant and rescue (on dithranols' irritation) treatment has been studied (72-74). Though, the results of these studies are highly contradictory. Said so, a clear evidence based recommendation for the use for local steroids as a pre-, concomitant and rescue (on dithranols' irritation) treatment is currently not available.

However, at least in my clinical experience the short-term use of local steroids in case of a severe dithranol irritation was effective and sufficient enough to control the inflammatory symptoms.

2.2.7.2 Staining

In addition to the irritation, a browning of lesional and perilesional skin occurs frequently and may persist up to 6 weeks after end of dithranol treatment (1). If soft textiles are contaminated with dithranol, a permanent brownish discoloration may occur (1).

The brownish discoloration is based on the oxidation of dithranol to inert brown compounds which have the capacity to attach on keratin, synthetic- and natural fibers (40).

2.2.7.3 Further local side effects

Allergic contact dermatitis, (toxic) blistering, necrosis or postinflammatory hypopigmentation are described as rare side effects of a dithranol treatment (75-79).

2.2.7.4 Pregnancy

According to a recent review, dithranol is suggested as a safe treatment option in localized plaque psoriasis and is rated as a category “C” drug in pregnancy (80). An area wide (>30% of the BSA) dithranol application in pregnancy is not recommended . However, the German S3 Guidelines for the treatment of psoriasis provides no clear evidence for the dithranol application in pregnancy due to lacking studies (1).

2.2.7.5 Toxicity

Animal models suggest a carcinogenic potential for irritants including dithranol. Though an association between the use of local dithranol and an increased risk for skin cancer has (until now) not been shown (40). Moreover, after local application of dithranol it is not significantly traceable in the blood, which might explain the missing systemic side effects in the local use of this substance (50).

2.2.8 Therapeutic recommendations

Topical treatment options for psoriasis remain to be of high importance according to modern treatment guidelines (1, 20, 58, 81). The value of topical dithranol treatment is differently appraised. The authors of a British guideline recommend to consider short-contact dithranol treatment for resistant psoriasis of the trunk or limbs, whereas classical dithranol treatment is not mentioned (58). The experts of a German guideline discuss classical inpatient dithranol and short contact therapy extensively and recommend it for induction therapy in hospitalized patients with mild to moderate plaque psoriasis (1). However, evidence fails to show the superiority of one type of dithranol regimen over the other. In contrast, in an American guideline dithranol therapy is described as a secondary treatment option (20).

Absolute contraindications for dithranol treatment are:

- erythrodermic psoriasis
- psoriasis pustulosa
- psoriatic skin lesions nearby eyes and mucous membranes

Relative contraindications (due to lacking studies) are:

- pregnancy
- the treatment of children and infants

However, controlled and head-to-head comparative trials of dithranol are scarce, the established evidence on its treatment efficacy is low and little data is available to which extent its use may improve PASI, nowadays considered as the standard parameter to monitor therapeutic success in treated psoriasis patients.

3 THESIS PART 1: THE EFFICACY OF CLASSICAL DITHRANOL THERAPY SHOWN BY PSORIASIS AREA AND SEVERITY RATE REDUCTION

AIMS

Psoriasis represents one of the most common chronic inflammatory skin diseases. Topical treatment options for psoriasis are still of high importance according to modern treatment guidelines. Controlled and head-to-head comparative trials of dithranol's therapeutic efficacy and/or PASI reduction rates, the present benchmark for scoring therapeutic efficacy in treatment of psoriasis patients, are scarce. The recommendations to administer topical dithranol differ among various national guidelines. The aim of the study was to investigate the efficacy of a classical inpatient dithranol therapy on PASI of psoriasis patients by analyzing data that were reported to the PsoRA.

Text of materials, results and discussion on Part I of the thesis **"THE EFFICACY OF CLASSICAL DITHRANOL THERAPY SHOWN BY PSORIASIS AREA AND SEVERITY RATE REDUCTION"** has been published in the British Journal of Dermatology:

Psoriasis Area and Severity Index 75 rate of classical inpatient dithranol therapy under daily life conditions (82)

C. Painsi, M. Patscheider, M. Inzinger, R. Huegel, B. Lange-Asschenfeldt, F. Quehenberger, P. Wolf

British Journal of Dermatology 2015; 173, 815-7.

3.1 Material and methods

3.1.1 Study setup

The data analyzed retrospectively in this study were collected at the Department of Dermatology, State Hospital Klagenfurt, from patients with psoriasis treated with CID alone or in combination with UVB 311nm radiation under daily life conditions between January 2007 and December 2012. At this department, CID was considered and given as the standard treatment for chronic plaque-type psoriasis until very recently. The clinical data were extracted from patient charts and reported to the PsoRA. The registry was approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10), and the retrospective analysis reported here was approved by the accountable ethics committee of the Austrian federal state of Carinthia (application number MZ10/13). The study was conducted in accordance with the principles of the Declaration of Helsinki.

3.1.2 Treatment formulations and administration

The dithranol ointment formulations used by the patients whose data were analyzed were prepared extemporaneously (see below: formulations of dithranol ointment). Dithranol treatment was started at the lowest standard concentration (i.e., 0.1% [1:1000 ointment]) and administered once daily to lesional skin. The ointment remained on the lesions and was not washed off (in contrast to the short-contact dithranol treatment regimen). In general, the dithranol concentration of the topically applied ointment was increased every 2 days to a maximal concentration of 1% (1:100 ointment) as warranted by the skin irritation observed in the treated individual. In the case of very strong irritation upon dithranol treatment, dithranol was paused and in some cases topical steroids were administered for 1 to 2 days to the inflamed skin. Emollients were allowed ad libitum for skin care.

Formulations of dithranol ointment used in analysis population

Dithranol 1:100 (50 g) [1% ointment]

Dithranolum (0.50 g)

Salicylic acid (1.00 g)

Paraffinum liquidum (1.50 g)

Vaselinum album (47.00 g)

Dithranol 1:250 (50 g) [0.4% ointment]

Dithranolum (0.20 g)

Salicylic acid (1.00 g)

Paraffinum liquidum (1.30 g)

Vaselinum album (47.50 g)

Dithranol 1:500 (50 g) [0.2% ointment]

Dithranolum (0.10 g)

Salicylic acid (1.00 g)

Paraffinum liquidum (1.00 g)

Vaselinum album (47.90 g)

Dithranol 1:750 (50g) [0.16% ointment]

Dithranolum (0.08 g)

Salicylic acid (1.00 g)

Paraffinum liquidum (1.00 g)

Vaselinum album (47.93 g)

Dithranol 1:1000 (50 g) [0.1% ointment]

Dithranolum (0.05 g)

Salicylic acid (1.00 g)

Paraffinum liquidum (1.00 g)

Vaselinum album (47.95 g)

3.1.3 Efficacy and data analysis

The primary efficacy endpoint of the study was defined as a ≥75% reduction in PASI (PASI75) after treatment initiation. Baseline PASI was determined using routine photographs taken to document disease at patient admission for treatment. Efficacy (i.e., response to therapy) was documented in the discharge documents and maximally categorized as either PASI75 or early treatment termination. PASI determination and the extraction of the categorization of the PASI reduction was done by one of the investigators.

Categorizing a maximal response as PASI75 and not higher (i.e., PASI90 or complete remission) allowed for conservative analysis and for the scoring of any remaining redness after treatment, whether due to psoriasis or irritation from dithranol, as a psoriatic skin manifestation. Data regarding patient characteristics and comorbidities were obtained from screening hospital documents and discharge reports.

3.1.4 Statistical analysis

Descriptive statistics were used to report patient demographics and treatment characteristics at baseline. Potential predictive factors for PASI75 or early treatment termination (e.g., patient age, gender, disease duration, psoriasis type, baseline PASI, psoriasis family history, body mass index [BMI], and the presence of one or more comorbidities) were tested for statistical significance using Spearman correlation or the Kruskal-Wallis test. All statistical analyses were performed using R 2.15.3 statistical software (www.r-project.org). Statistical significance was set at a p-value of ≤ 0.05.

3.2 Results

3.2.1 Patient demographics

Data from 110 patients (75 men [68.2%] and 35 women [31.8%]) were analyzed retrospectively. The median patient age was 48.3 years (range, 13.4 to 97.7 years). The median body mass index (BMI) was 27.0 (range, 18.1 to 38.8). Psoriasis types included chronic plaque psoriasis in 77 patients (70%) and guttate psoriasis in 33 patients (30%). The median disease duration was 10.2 years (range, 0.1 to 84.0 years), and the median PASI at treatment initiation was 13. 0 (range, 2.8 to 40). A family history of psoriasis was reported in 28 patients (25.5%), no family history of psoriasis in 36 patients (32.7%), and uncertain family history in 46 patients (41.8%). Comorbidities included obesity in 40 patients (36.4%), fatty liver disease in 28 patients (25%), insulin- or non-insulin dependent diabetes mellitus in 16 patients (14.5%), hyperlipidemia in 16 patients (14.5%), arterial hypertension in 30 patients (27.3%), coronary heart disease in 6 patients (5.5%), and kidney disease in 3 patients (2.7%).

3.2.2 Treatment characteristics

CID was administered in the formulations described in 2.1.2. Seventy-seven patients (70%) received CID alone, and 33 patients (30%) received CID in combination with UVB 311nm irradiation. The median number of UV exposures was 5 (range, 1 to 11). Other than a between-group difference in the relative percentage of patients with plaque vs. guttate psoriasis (i.e., 75.3% vs. 24.7% in the monotherapy group, compared with 57.6% vs. 42.4% in the combination therapy group; p = 0.0727 Fisher's exact test), there were no major differences in clinical characteristics between the treatment groups.

3.2.3 Efficacy

Ninety-one patients (82.7%) completed treatment with CID and achieved PASI75 (Figure 1). The median time to PASI75 was 14 days (range, 3 to 25 days). In 19 patients (17.3%), treatment with CID was terminated early (i.e., before achieving PASI75) for reasons including lack of efficacy (i.e. PASI reduction by less than 50% [PASI<50] after at least 10 days of therapy; 5 patients, 4.5%); local irritation (burning sensation of the skin and erythema) (3 patients, 2.7%); and patient decision (11 patients, 10%). The median time to early treatment termination in those 19 patients was 5 days (range, 2 to 19 days) (Figure 1). Analysis revealed no difference in the rates of efficacy (i.e., PASI75) and early treatment termination between the monotherapy and combination (irradiated) treatment group (data not shown) and therefore they were pooled together for analysis.

3.2.4 Predictive factors

There was a weak but statistically significant (p=0.0011) positive correlation between baseline PASI and time to PASI75 (Figure 2). This became particularly evident for patients with a PASI below 10 at start of treatment, as visualized by the strong slope of the lowess line for this range in Figure 2. The median time to reach PASI75 was 10.2 days in patients with PASI below 10 (n=30) and 13.6 days in patients with PASI greater than 10 (n=61) (p=0.00062; Wilcoxon test). Conversely, other factors such as patient age, gender, disease duration, psoriasis type, BMI, and comorbidities showed no statistically significant correlation with either PASI75 or early treatment termination.

3.3 Figures

Figure source: Painsi et al. BJD 2015 (82)

Figure 1. Time-dependent PASI75 rate and early treatment termination rates. Ninety-one patients (82.7%) experienced a ≥75% reduction in PASI (PASI75) after treatment initiation (median time to PASI75, 14 days). Nineteen patients (17.3%) did not reach PASI75.

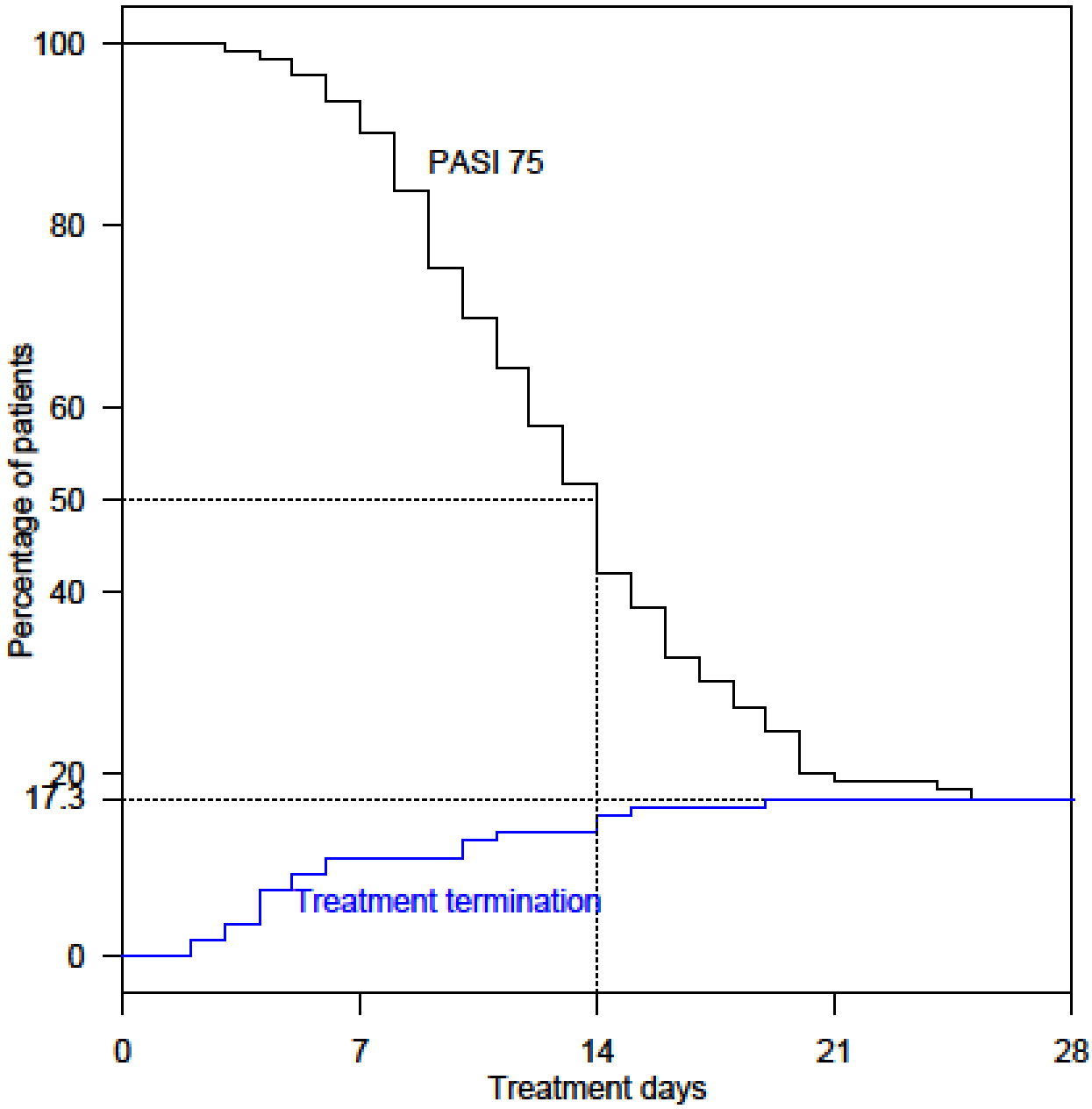
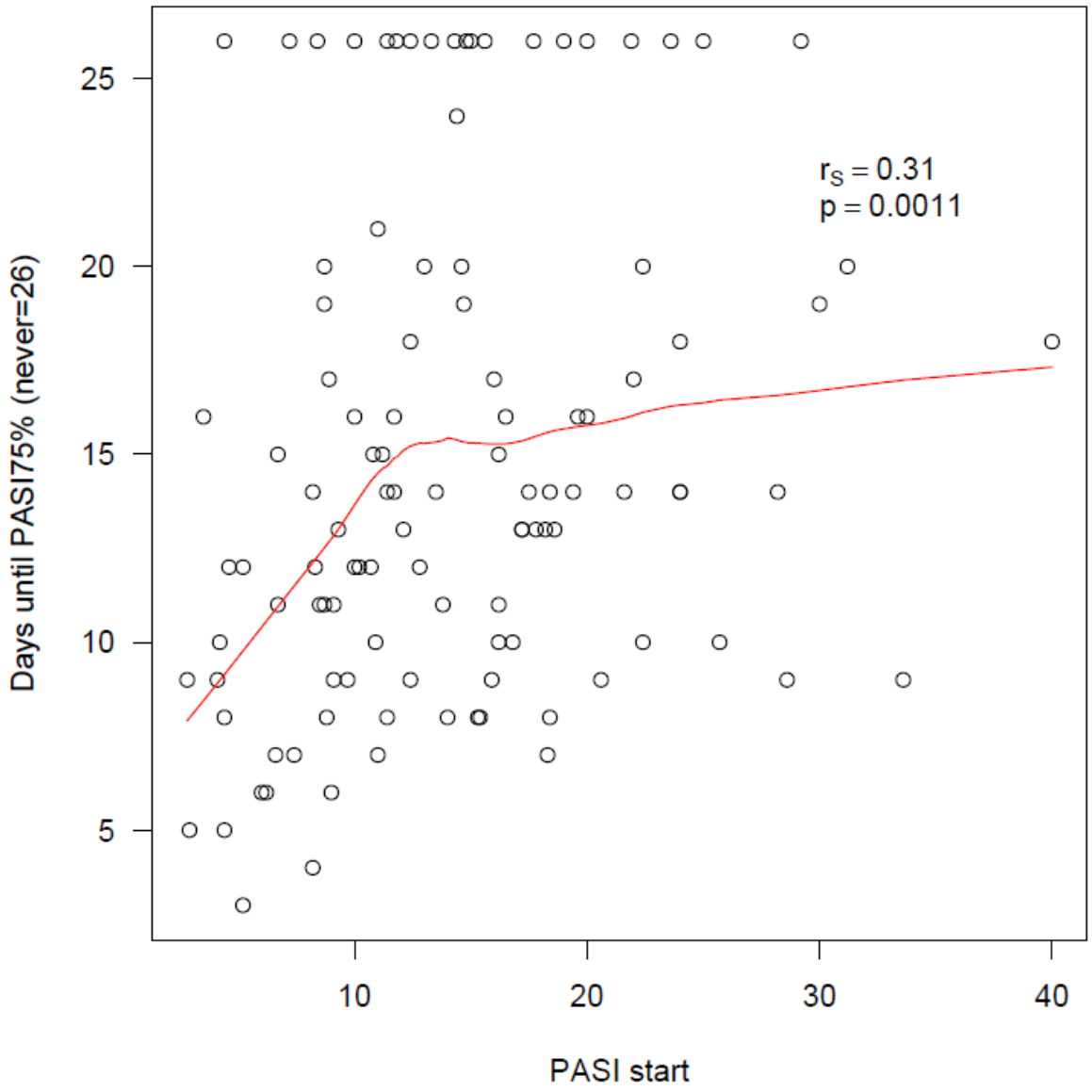


Figure source: Painsi et al. BJD 2015 (82)

Figure 2. Correlation between baseline PASI and time to PASI75. Note that 19 patients did not reach PASI 75. They were coded as 26, which is beyond the highest observed duration to conversion. The Spearman correlation coefficient (r_S) does not depend on the choice of the code of 26 since its calculation is based on the ranks of data only. The positive correlation of the data is visualized by the lowess line in red color, which is a robust nonparametric data smoother.



4 THESIS PART 2: THE PATIENT PERSPECTIVES AFTER A CLASSICAL DITHRANOL THERAPY

AIMS

CID is a highly effective topical antipsoriatic treatment option without any known systemic and long-term local side effects. Published psoriasis patient surveys suggest that a notable number of patients believe that their treatment is not aggressive enough. Many of these patients used topical treatments, which they assessed as time consuming, expensive, and as an ineffective approach to provide relief. Data, focusing explicitly on the patient perspectives after a dithranol have not been available. In the second part of the thesis we provide information, throughout a telephone interview survey, on the patient perspectives with respect to satisfaction, efficacy, adverse effects, and recurrence-free interval after a CID. Furthermore, patient perspectives were correlated with objective assessment parameters such as PASI.

Text of materials, results and discussion on Thesis part 2 “THE PATIENT PERSPECTIVES AFTER A CLASSICAL DITHRANOL THERAPY” has been published in the in the Journal of the German Society of Dermatology:

Patient perspectives on treating psoriasis with classical inpatient dithranol therapy: a retrospective patient survey (83)

C. Painsi, M. Patscheider, M. Inzinger, B. Lange-Asschenfeldt, F. Quehenberger, P. Wolf

Journal of the German Society of Dermatology 2015; 13, 1156-63.

4.1 Material and methods

4.1.1 Study setup

One hundred and ten patients with psoriasis were envisioned to be contacted in this survey (figure 1); their PASI75 response rates to CID have been reported in a previous publication (82). Between January 2007 and December 2012, the patients had been treated- under everyday conditions with CID monotherapy or in combination with UVB (311 nm) phototherapy at the Department of Dermatology, State Hospital Klagenfurt, Austria. The types of dithranol preparations used and their application have previously been described (82). With respect to the study population, the PsoRA was used to obtain demographics, treatment characteristics, and CID efficacy assessment by means of PASI improvement.

Through telephone interviews using a specific questionnaire, patient perspectives on CID were assessed by two of the investigators (C.P., M.P.) in June 2013. Prior to conducting the interviews, oral patient consent was obtained during the telephone calls. No incentives were offered. The interview questions were part of a questionnaire with predefined specific answers that covered ten items relating to satisfaction, efficacy, and adverse effects of CID. Answers were given on a four-or five-point ordinal scale and included i) ‘not assessable’ or ‘not present’, ii) ‘not correct at all’ or ‘minimal’, iii) ‘partly correct’ or ‘moderate’, iv) ‘mostly correct’ or ‘substantial’, and v) ‘fully correct’ or ‘maximal’) (Figure 2). The interviewing physician recorded the patients answers to these questions. Moreover, he documented the recurrence free interval after CID (in months) as recalled by each patient as well as the number of previous CID therapy cycles.

The registry and questionnaire used was approved by the Ethics Committee of the Medical University of Graz (application number 21-094 ex 09/10). The current study was granted by the Ethics Committee of the Federal State of Carinthia (application number MZ10/13) and conducted in accordance with the principles of the Declaration of Helsinki.

4.1.2 Statistical analysis

Descriptive statistics were used to provide baseline patient demographics. For statistical analysis, the results of “fully correct” and “mostly correct” as well as “maximal” and substantial were combined (as shown in Figure 2). Potential predictive factors affecting patient perspectives such as patient age, gender, disease duration, psoriasis type, baseline PASI, psoriasis family history, body mass index (BMI), and the presence of one or more comorbidities were tested with Spearman rank correlation or Kruskal-Wallis test. Kaplan-Meier-estimator was used to plot the recurrence-free interval after therapy. All statistical analyses were performed using R 2.15.3 (www.r-project.org). Statistical significance was set at a p-value of ≤ 0.05

4.2 Results

4.2.1 Patient demographics and treatment characteristics

We were able to collect data from 63 (57.2%) of the 110 patients (41 men [65.1%] and 22 women [34.9%]) (Figure 1). Demographic details and treatment characteristics of the enrolled patients are depicted in the Table 1. Comorbidities included obesity in 25 patients (39.7%); fatty liver disease, in 18 patients (28.6%), insulin- or non-insulin dependent diabetes mellitus in 9 patients (14.3%); hyperlipidemia in 14 patients (22.2%); arterial hypertension in 17 patients (27.0%); coronary artery disease in four patients (6.3%); and kidney disease in two patients (3.2%).

4.2.2 Efficacy

Fifty-two of the 63 patients (82.5%) completed CID treatment and achieved PASI75 (Table). The median time to PASI75 was 12.5 days (range, 3 to 25 days). In 11 patients (17.5%), CID treatment was discontinued prematurely (i.e., before achieving PASI75) for reasons such as lack of efficacy (i.e. PASI reduction by less than 50% [PASI<50] after at least ten days of therapy; (4 patients, 6.3%); local irritation (burning sensation of the skin and erythema) (1 patient, 1.6%); and patient request (6 patients, 9.5%). The median time to premature discontinuation of treatment in these eleven patients was five days (range, 2 to 19 days). Not considering residual redness after dithranol exposure at the end of a treatment course as potential psoriatic erythema, as many as 51 (80.9%) patients in this analysis may have experienced a PASI reduction of 90% (PASI90). Statistical analysis revealed no significant difference in the rates of efficacy rates (i.e., PASI75 or PASI90) and premature treatment discontinuation between the monotherapy and combination (additional UVB 311 nm phototherapy) treatment groups (Table 1).Similar to our previous publication (82), pooled data was therefore used in the analysis. Importantly, ten out of twelve (83%) patients showed a satisfactory response to CID (PASI75 or greater reduction) despite the fact that they had previously failed to adequately respond to systemic therapy including methotrexate, oral retinoids, cyclosporine, fumaric acid, or ustekinumab. Treatment in these patients (n=12) had been stopped due to inefficacy (1 patient with fumaric acid, 3 patients with methotrexate [one of these patients had additionally received systemic corticosteroids and one other oral retinoids], and 3 patients with oral retinoids) or side effects such as hepatotoxicity (1 patient with methotrexate), nausea (2 patients with methotrexate), nephrotoxicity (patient with cyclosporine) or disease exacerbation (the patient with ustekinumab.

4.2.3 Patient perspectives on satisfaction, efficacy, and treatment adverse effects

The results with respect to patient perspectives are summarized in Figure 2. Thirty-seven out of 60 patients (6.7%) were overall satisfied after CID (i.e. answer, mostly or fully correct) (not assessable [n.a.], 3 [5%]). CID was deemed effective by 44 of 57 (77.2%) patients (n.a., 6 [10.5%]). Thirty-two of 48 (66.7%) patients responded that CID treatment was more effective than their prior therapy (n.a.,15 [31.3%]). The cosmetic result after CID was rated as very good by 44 of 60 (73.3%) patients (n.a.,3 [5.0%]). The irritant response of lesional and perilesional skin due to CID was considered substantial or maximal by 12 of 61 (19.7%) patients (n.a.,2 [3.3%]). Six of 61 (9.8%) patients assessed the brownish discoloration of lesional and perilesional skin after CID as substantial or maximal (n.a.,2 [3.3%]). Thirty-two of 58 (55.2%) patients reported no other adverse effects (n.a.,5 [8.6%]).; 33 of 58 (56.9%) patients considered CID time- consuming (n.a.,5 [8.6%]).; six of 57 (10.5%) patients reported other disadvantages (n.a.,6 [10.5%]). Altogether, 42 of 57 (73.7%) patients would recommend CDI for further treatment (n.a.,6 [10.5%]).

4.2.4 Recurrence-free interval and number of CID therapy cycles

Patients reported a median recurrence-free interval of four months (95% confidence interval [CI] 3-9 months) after CID (Figure 3). In 22 (34.9%) patients, CID had previously been applied. Those patients had received a mean of 2.6 previous CID therapy cycles.

4.2.5 Predictive factors

Statistical analysis showed a significant negative correlation (rho =-0.40; p=0.0018) between the baseline PASI and the patients' perception of the irritant response of lesional and perilesional skin caused by CID therapy (Figure 4). A positive correlation was found between the patients' perception of the amount of time invested in CID treatment and the days until reaching PASI75 (rho=0.30; p=0.017). The patients' recommendation for CID (p=0.018) and patients' overall satisfaction after CID (rho =0.38 ; p=0.012) was positively correlated with the recurrence-free interval.

Other factors, such as patient age, gender, disease duration, psoriasis type, psoriasis family history, body mass index (BMI), comorbidities (obesity, liver diseases, diabetes mellitus, hyperlipidemia, arterial hypertension, coronal disease, kidney disease), previous systemic treatments as well as phototherapy, the number of previous CID cycles, and the recurrence-free interval showed no impact on the patient perspectives (data not shown).

4.3 Figures

Figure source: Painsi et al. JDDG 2015 (83)

Figure 1. Flow-chart of patient enrollment.

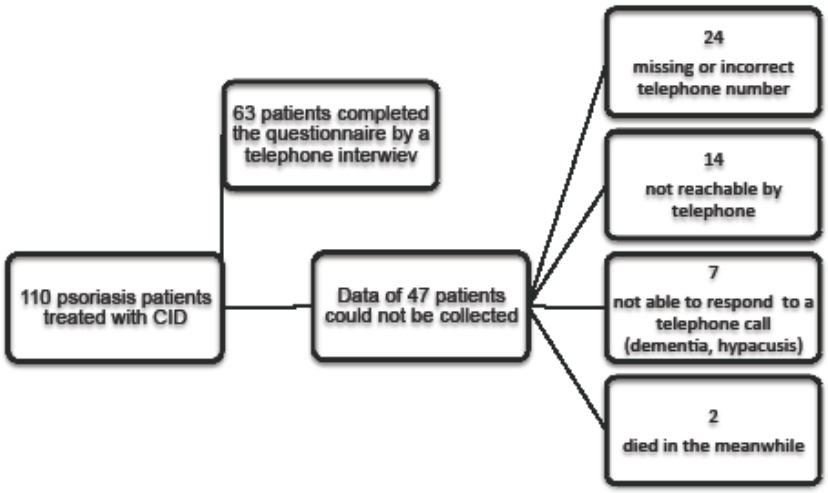


Figure source: Painsi et al. JDDG 2015 (83)

Figure 2. Results of the answers to ten questions on patient satisfaction, efficacy, adverse effects of CID. The bars right to 0%-axis represent the portions of patients answering to a specific question on the four [A]/ five [B]-point ordinal scale. The percentages plotted in the bar chart of the figure indicate the portion of answers of fully correct or mostly correct and substantial or maximal, respectively, taken together. The bars left to the 0%-axis [A] represent the percentages of patients who answered a specific question with "not appraiseable" (which where therefore excluded from the analysis).

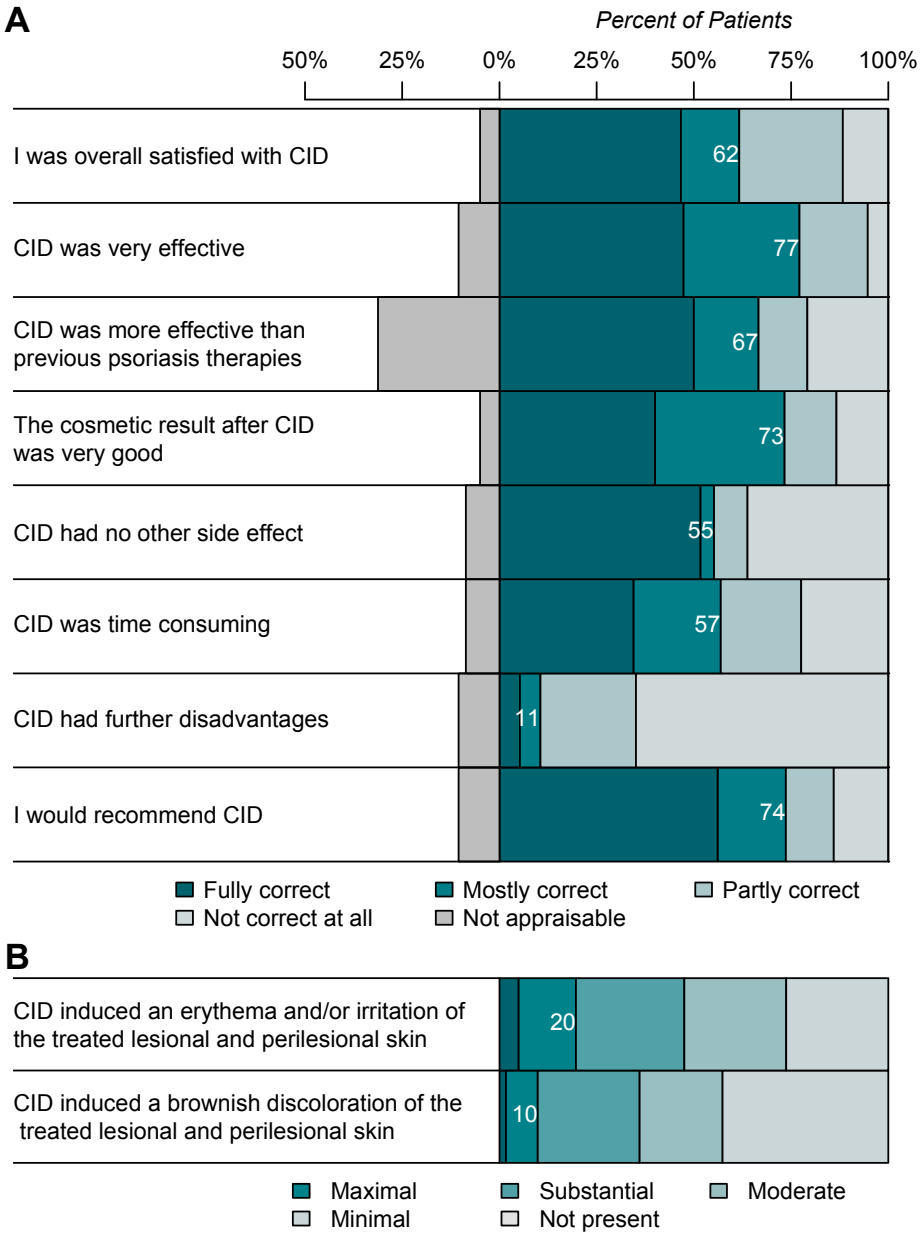


Figure source: Painsi et al. JDDG 2015 (83)

Figure 3. Relapse-free interval after CID treatment. Median and 95% confidence intervals are shown. The median time to relapse was 4 months (dashed line).

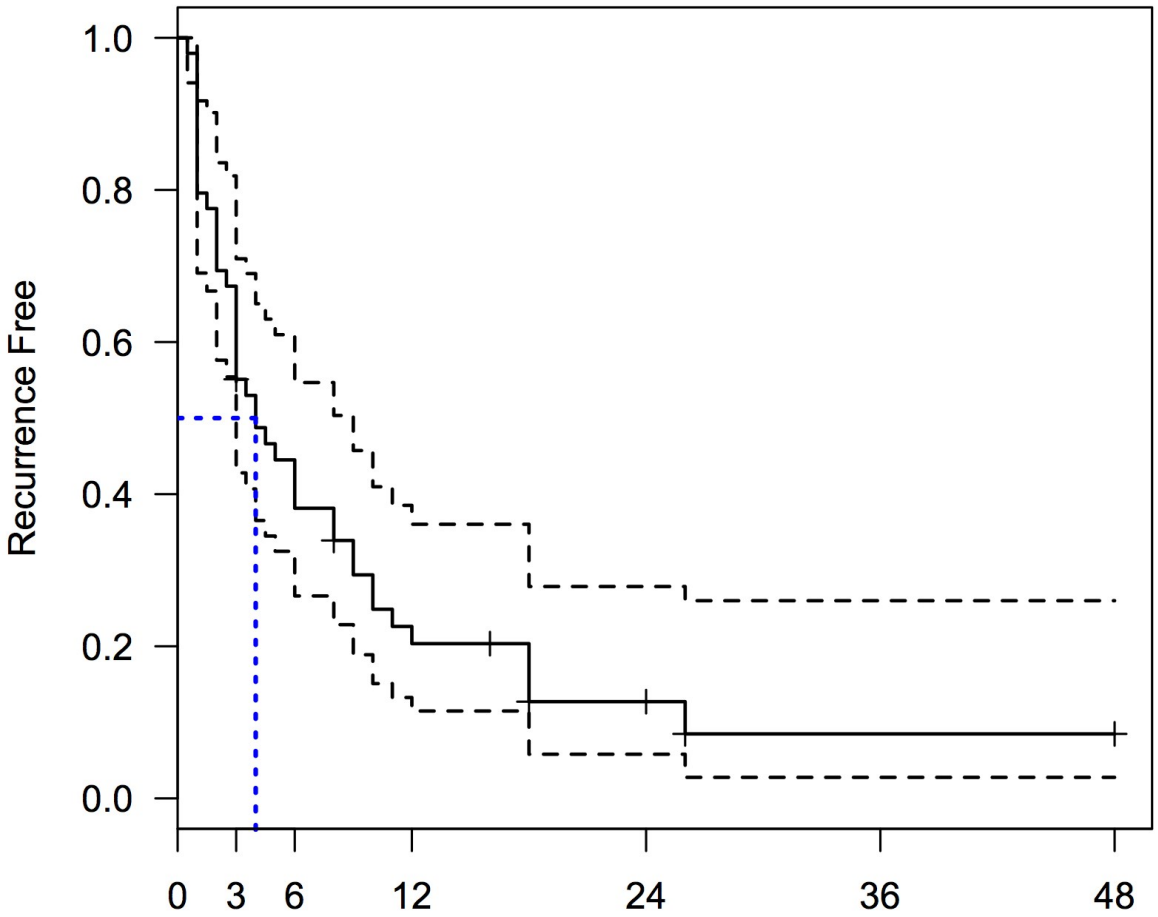


Figure source: Painsi et al. JDDG 2015 (83)

Figure 4. Correlation between baseline PASI and the patient assessment for the irritant response of lesional and peri-lesional skin due to CID.

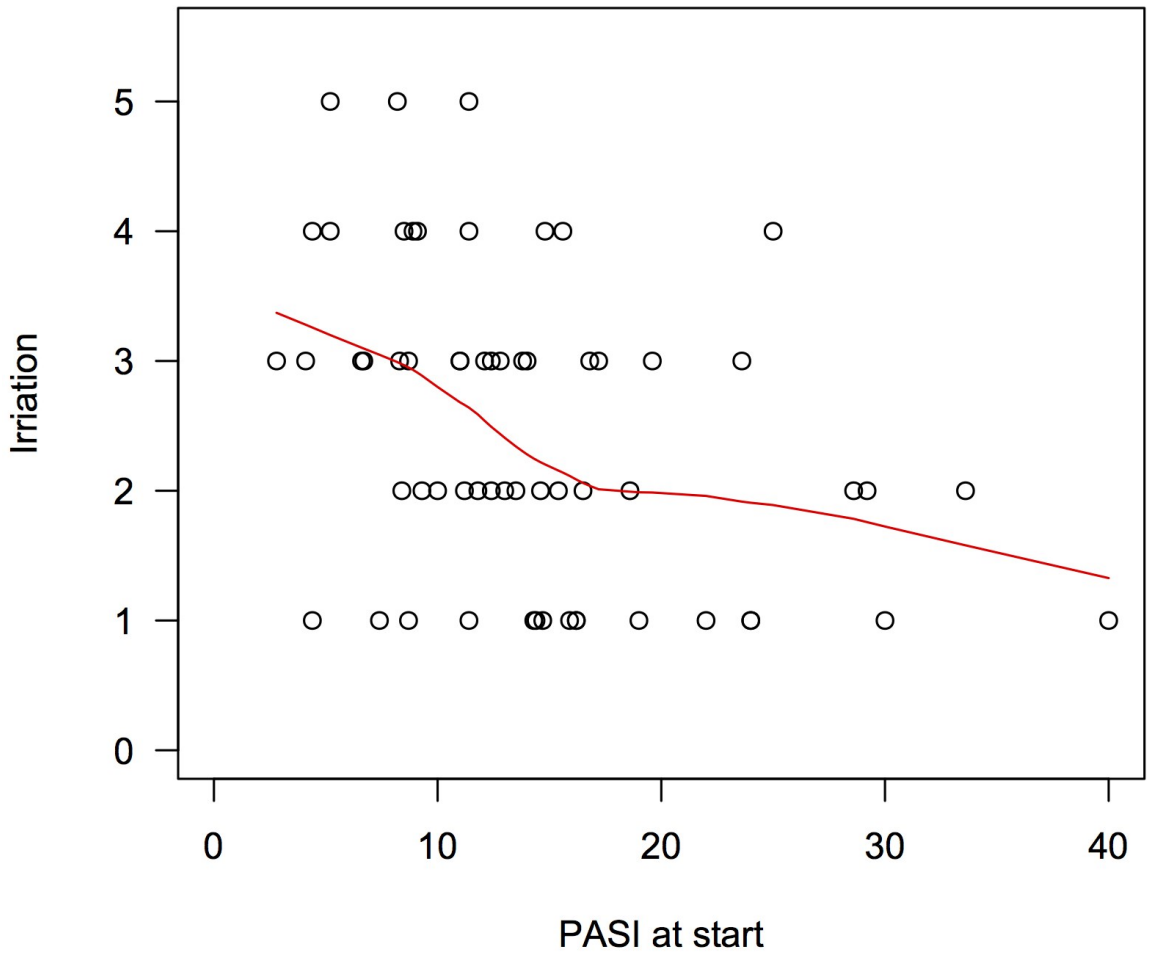


Figure source: Painsi et al. JDDG 2015 (83)

Table. Patient and treatment characteristics

Characteristic		**Dithranol**	**Dithranol plus UVB311nm**	**All treatments**
No. of patients (%)		40 (63.5)	23 (36.5)	63 (100)
Median age in years (range)		49 (13 -83)	52 (18 -74)	49 (13 -83)
Men/ women, n (%)		28 (70.0) / 12 (30.0)	13 (56.5) / 10 (43.5)	41 (65.1) / 22 (34.9)
Median duration of psoriasis in years (range)		15 (0.2 - 67)	6.6 (0.1 -56)	14.2 (0.1 -67)
Type of psoriasis	Plaque, n (%)	32 (80.0)	15 (65.2)	47 (74.6)
	Guttate, n (%)	8 (20.0)	8 (34.8)	16 (25.4)
Median baseline PASI (range)		13 (2.8-34)	12 (4.4 -40)	12.9 (2.8-40)
Median UVB 311 nm radiation exposures (range)		-	4 (1-14)	0 (0-14)
PASI response	PASI90, n (%)	33 (82.5)	18 (78.2)	51 (80.9)
	PASI75, n (%)	33 (82.5)	19 (82,6)	52 (82.5)
Median time in days until reaching PASI (range)	PASI90	12 (3 -25)	14.5 (5 -24)	12.5 (3 -25)
	PASI75	12 (3 -25)	15 (5 -24)	12.5 (3 -25)
Patient number of therapy termination, n (%)	Total, n (%)	7 (17.5)	4 (17.4)	11 (17.5)
	Patient decision	3 (7.5)	3 (13.0)	6 (9.5)
	Lack of efficacy	4 (10)	0 (0)	4 (6.3)
	Dithranol irritation	0 (0)	1 (4.3)	1 (1.6)
Mediantime in days until therapy determination (range)	Total	10 (2 -19)	4 (2 -11)	5 (2 -19)
	Patient decision	4 (2 -5)	4 (4 -11)	4 (2 -11)
	Lack of efficacy	14 (10 -19)	-	14.5 (10-19)
	Dithranol irritation	-	2 (2 -2)	2 (2 -2)

4.4 Discussion

Our retrospective analysis of the PASI reduction shows that CID is a highly effective treatment for chronic plaque and gutatte psoriasis. In our hands, CID resulted in PASI75 in 82.7% of treated patients within a median of 14 days after treatment initiation; conversely, treatment was terminated early (a median of 4 days after initiation) in 17.3% of patients due to lack of efficacy, local skin irritation, or patient decision. Indeed, not considering residual redness after dithranol exposure at the end of a treatment course as potential psoriatic erythema, as many as 89 (80.9%) of the patients in this analysis may have experienced a reduction of PASI by 90% (PASI90) (data not shown).

The patient perspectives survey revealed that a high percentage (77%) of patients rated CID as very effective. Moreover, combining the answers “fully” and “mostly correct” in the analysis, more than 60% of patients were satisfied with CID, and 73% assessed the cosmetic result as very good (thesis part II, Figure 2). Seventy-four percent of patients would recommend CID as anti-psoriatic treatment. Conversely, data also showed the well-known CID therapy limitations (such as amount of time required, CID-related irritation, and brownish skin discolorations). The negative correlation between baseline PASI and the patients’ assessment of the irritant response of lesional and perilesional skin caused by CID suggested that a lower baseline PASI may be associated with a more sensitive assessment and/-or a higher risk for the irritant response to CID (thesis part II, Figure 4). Patients recalled a median recurrence-free interval of four months after CID (with a statistical CI of 3 to 9 months) (thesis part II, Figure3). Statistical correlation analysis revealed that the recurrence-free interval was positively correlated with the patients’ recommendation of CID.

Our efficacy rate (but not the treatment duration) compares well to that reported in the literature. Swinkels et al.(84) reported a PASI75 rate of 81.7% in CID-treated patients but a median time to PASI75 of 37 days, twice the duration found in our analysis. Two explanations may account for this difference in the treatment durations reported by us and by Swinkels’ group. The first possible explanation is the difference in dithranol concentrations used. The patients in our analysis population started

treatment with a formulation containing 0.1% dithranol and a salicylic acid add-on (85) (see Supplementary Table, thesis part I) and had their dithranol concentration increased every 2 days (to a maximum of 1.0%) depending on the level of skin irritation; conversely, the patients in the study reported by Swinkels et al. started treatment with a formulation of 0.05% dithranol in petrolatum only and had their dithranol concentration increased every 3 days (to a maximum of 5.0%). The second possible explanation for the considerably longer treatment duration reported by Swinkels et al. is the higher mean baseline PASI of 18.2 in their analysis versus 13.2 in our analysis. This possibility is supported by the direct correlation we observed between baseline PASI and time to PASI75 (thesis part I, Figure 2).

Evidence on the relapse rates of CID therapy is remarkably low (40). Compared to baseline, Kirkup et al reported a sustained reduction of the mean lesional surface area of 74% in the once-daily treatment group vs. 52% in the twice-daily treatment group in psoriasis patients, six month after they had initially achieved clearance or near clearance following CID treatment (86). It is difficult to do compare the results of our survey with previous studies, since the questions we posed were meant to assess the time until the initial signs of recurrence rather than the percentage of cleared skin area in (partially) sustained response.

So how do recurrence rates of CID compare to those of other treatment modalities? Langley et al. reported that the median time to relapse (defined as a reduction in the PASI improvement from baseline of at least 50% after achieving clearance ore near-clearance) after calcipotriol plus betamethasone dipropionate and tacalcitol ointment was 63 and 61 days, respectively (87). By contrast, with a median of four months, the recurrence-free interval after CID was nearly twice as long. In chronic plaque psoriasis, Yones et al. reported a median time to relapse (defined as a reduction in the PASI improvement from baseline [mean baseline PASI 10.75] of at least 50% after achieving clearance or ore almost clearance) of four months after narrowband UVB vs. eight months after psoralen plus UVA (88). Finally, with respect to biologics a review by Monique Kamaria et al. indicates a median time to loss of PASI50 after discontinuing ustekinumab of approximately 62 weeks and after adalimumab between 12 and 24 weeks (89).

General drawbacks to dithranol therapy are its practicality, associated staining of skin and clothing, and high rate of local irritation (up to 85%, as reported by Kucharekova

et al. (71)). That said, a recent study comparing quality of life in patients receiving topical vitamin D3 derivative calcipotriol and dithranol concluded that, despite their equal improvement of quality of life, calcipotriol is more practical and patient friendly and thus can be considered a first-line therapeutic option in clinical practice. However, in patients recalcitrant to calcipotriol and other topical treatments, preference should be given to the dithranol regimen (90).

The patient sample that we analyzed in our studies is representative of a general psoriatic population. Most of the demographic and disease characteristics of our sample (e.g., relative distribution of guttate psoriasis vs. chronic plaque psoriasis; family history of psoriasis; and prevalence of comorbidities such as arterial hypertension, hyperlipidemia, coronary heart disease, diabetes mellitus, and obesity) are consistent with those reported from a global psoriasis registry of 11,900 patients (the Psoriasis Longitudinal Assessment and Registry [PSOLAR]) (91), while others (male to female ratio, prevalence of liver diseases with 4.1% in PSOLAR) differ.

The major limitation of our analysis was its observational retrospective design with its PASI calculation based on photographic documentation and non-anonymously conducted telephone interviews. Another potential limitation is the limited cohort size and our decision to pool data on the results of CID alone or in combination with 311nm UVB. We decided to pool the data because we found no difference in the efficacy rates and the rates of premature discontinuation of treatment between the monotherapy and the combination (UVB 311nm phototherapy) therapy groups. This may have been to the, on average, relatively small number of patients receiving UVB therapy. Alternative explanations include the non-randomized treatment allocation and the possibility that combination therapy was used in more difficult-to-treat patients

Taken together, the results of our retrospective analysis contributes to the recently reviewed level of evidence for dithranol's antipsoriatic efficacy (40) and indicates that CID remains one of the most effective antipsoriatic treatment options. In particular, the treatment formulations (i.e., 0.1-1% dithranol combined with 1% salicylic acid) (85) and regimen we used may lead to faster remission of psoriasis than that achieved with any other currently available topical and/or systemic modalities in the antipsoriatic armamentarium, including conventional agents (92) and biologics that block tumor necrosis factor-α(93) or IL-12/23 (93, 94). Indeed, in terms of efficacy

and time to remission, CID may even be able to compete with, if not outperform, the latest generation of Th17-blocking biologics (95-97).

The results of our patient perspective survey show that, despite the known disadvantages of the treatment- such as time required, lack of sustainable disease control, as well as skin irritation and discoloration- patients overall assessed CID as an effective anti-psoriatic treatment option providing satisfaction in a large percentage of patients. This is in contrast to the patient assessment of other topical treatment modalities in general, as reported by Krueger et al. (98).

Indeed, psoriasis patients obtaining biologics are usually much more satisfied than those receiving other treatments including topical agents (and conventional agents)

Nonetheless, together with the recommendations of other investigators (1, 71, 90), our studies indicates that dithranol remains a valuable treatment option especially as induction therapy in day or inpatient care. Importantly CID (similarly to Goeckermann regimen) (99) may be also effective in patients who failed to respond to systemic therapy, including traditional agents and biologics.

4.5 Prospects

Dithranol triggers an inflammatory reaction of that kind, that one would assume inflammatory psoriatic skin changes in the sense of a "Köbner phenomenon". However, due to the inflammatory response a potent anti-psoriatic effect without systemic side effects is caused. (1, 40, 82, 100) Furthermore, clearing of psoriatic skin changes of both treated and untreated skin could be observed under dithranol therapy. The exact mechanisms of the substance's anti-psoriatic effect, however, are not elucidated to date (40).

Another unresolved aspect in connection with psoriasis vulgaris lies in the role of blood and lymph vessels and also their growth factors. Observations showed that angiogenesis inhibitor-therapy (e.g. bevacizumab) of oncogenic patients, which also suffered from psoriasis vulgaris, led to a clearing of psoriatic skin changes (101). In psoriasis affected areas a higher vessel density with convoluted and dilated blood vessels become histopathologically apparent (102). The effect of a topical dithranol therapy on above-mentioned vascular changes and also on blood and lymph vessel-specific growth factors has not been investigated yet to date.

It is known, however, that an abnormal T cell-transmitted immune regulation plays a significant role in the pathogenesis of psoriasis vulgaris. Owing to these findings numerous psoriasis-specific, T cell activating cytokines such as IL-17, -23 and TNF alpha could be identified(103).

Therefore, a clinical study was set up to study the inflammatory reaction under and after a topical dithranol therapy as well as the influence of the therapy on pro- and contra-inflammatory molecules. In addition a possible role of microRNAs in gene expression of inflammation factors shall be explored. MicroRNAs belong to the biggest gene family and represent approximately 1% of the total human genome. They are part of the class of "small non-coding RNAs" and have an approximate length of 22 nt. To date almost 3000 microRNAs are known; they are largely evolutionary conserved. They post-transcriptionally regulate over 50% of the human genes(104, 105). MicroRNAs are differentially expressed in various organs and tissues. Their coding genes are often situated in the intron of the regulating gene, in the promoter region of those genes or in separate DNA sections. Important for the

inhibiting effect of microRNA is the so called "seed sequence" which is a section of approximately 7 nt in length; it is situated in the 5’ region complementary to the microRNA of the regulating gene. One microRNA often pathway-specific regulates up to 300 different genes and in reverse one gene can be influenced by numerous unrelated microRNAs. MicroRNAs admittedly operate intracellularly by bonding to other microRNAs, but sometimes they will be packed into exosomes, secreted into the blood circulation and absorbed by peripheral cells, in which they unfold their effect far away from the point of origin. As the aetiology of psoriasis is multifactorially and multi-genetically, it is therefore no surprise that a large number of microRNAs were described playing a role during the pathogenesis of psoriasis: the microRNAs 207 320, 99a, 150, 197, 203, 220, 423 and others (106, 107). The biosynthesis of microRNA 206, for instance, is controlled by AP-1, which is a heterodimeric complex composed of c-Jun and c-Fos. Normally AP-1 regulates the expression of numerous cytokines resulting from stress factors and infections. It is important for this purpose that the genes of microRNAs 206 and 133b are within the promoter vicinity of IL-17 and that those three genes are regulated coordinately, i.e. are co-transcribed (108). It appears to be plausible that the effect of dithranol is at least partially achieved by the influences of microRNAs.

In addition, the effect of dithranol on blood- and lymph vessels and their regulating growth factors shall be investigated.

A study protocol entitled “Study on therapeutic mechanisms of dithranol therapy with regard to pro –and contra- inflammatory factors, microRNA and also lymph and blood vessels in patients with chronic plaque psoriasis has been approved by the ethics committee of the federal state of Carinthia (application number A 23/15). The data will be published elsewhere.

THESIS CONTRIBUTIONS

Clemens Painsi wrote the dissertation and drafted the figures presented in here.

Contribution to the thesis parts

Thesis Part 1:

THE EFFICACY OF CLASSICAL DITHRANOL THERAPY SHOWN BY PSORIASIS AREA AND SEVERITY RATE REDUCTION

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"Psoriasis Area and Severity Index 75 rate of classical inpatient dithranol therapy under daily life conditions" (82)

C. Painsi, M. Patscheider, M. Inzinger, R. Huegel, B. Lange-Asschenfeldt,

F. Quehenberger, P. Wolf

C.P. and P.W. designed the research.

C.P. collected the data at the study subcenter of the Department of Dermatology, State Hospital Klagenfurt and reported them to the PsoRA.

M.I. und R.H. helped in the setup of the participation of the Department of Dermatology, State Hospital Klagenfurt in PsoRA.

M.P. helped with the data collection and reporting to PsoRA.

B.L-A. supervised the research activities in Klagenfurt.

F.Q. provided the statistical analysis of the data and produced figures.

C.P. performed the major part of the data extraction for the figures and tables shown and drafted the publication and the thesis.

Jude Richard, Austin, TX, U.S.A. edited the text of the manuscript published in the British Journal of Dermatology.

All authors approved of the submitted versions and final version of the manuscript published in the British Journal of Dermatology.

P.W. supervised the overall research and revised the text materials.

Thesis Part 2:

“THE PATIENT PERSPECTIVES AFTER A CLASSICAL DITHRANOL THERAPY”

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“Patient perspectives on treating psoriasis with classical inpatient dithranol therapy: a retrospective patient survey” (83)

C. Painsi, M. Patscheider, M. Inzinger, B. Lange-Asschenfeldt, F. Quehenberger, P. Wolf

C.P. and P.W. designed the research.

C.P. collected the data at the study subcenter of the Department of Dermatology, State Hospital Klagenfurt and reported them to the PsoRA.

M.I. helped in the setup of the participation of the Department of Dermatology, State Hospital Klagenfurt in PsoRA.

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F.Q. provided the statistical analysis of the data and produced figures.

C.P. performed the major part of the data extraction for the figures and tables shown and drafted the publication and the thesis.

H. N. Ananthaswamy, Houston, TX, USA, critically read the manuscript published in the Journal of the German Society of Dermatology.

All authors approved of the submitted versions and final version of the manuscript published in the British Journal of Dermatology.

P.W. supervised the overall research and revised the text materials.

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