Diplomarbeit

Cutaneous side effects of TNF- alpha inhibitors

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Ort, Datum …….. (Unterschrift)

Affidavit

Herewith I, Aline Kos, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.

Graz, Juli 2012

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Abbreviations

AA	Alopecia Areata
ADA	Adalimumab
ALCL	Anaplastic large- cell Lymphoma
ANA	Antinuclear antibodies
AS	Ankylosing spondilits
AZA	Azathioprine
BAFF	B-cell activating factor
BSRBR	British Society for Rheumatology Biologics Register
CD	Cohn's disease
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CD30	Cluster of Differentiation 30
CD40L	CD40 Ligand
CD81	Cluster of Differentiation 81
CPP	Chronic plaque psoriasis
CTCL	Cutaneous malignant neoplasms Lymphoma
CXCR3	Chemokine (C-X-C motif) receptor 3
DMARD	Disease-modifying anti-rheumatic drugs
DNA	Desoxyribonucleic acid
dsDNA	double-stranded DNA
e.g.	exempli gratia
EMEA	European Medicines Agency
ERAP 1	endoplamatic reticulum aminopeptidase
Etan	Etanercept
Fab	Fragment antigen binding
FasL	Fas Ligand
FDA	Food and Drug Administration
GA	Granuloma annulare
GTP	Guanosine Triphosphate
GWAS	genome wide association scans
HSV	Herpes simplex virus

IBD	Inflammatory Bowel Disease
IgG1	Immunoglobulin 1
IGD	Interstitial granulomatous dermatitis
IGM	Immunoglobulin M
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1-beta
IL-6	Interleukin- 6
IL 12	Interleukin 12
IL17	Interleukin 17
IL18	Interleukin 18
IL 23	Interleukin 23
IL-23R	Interleukin 23 Receptor
INF	Infliximab
JIA	Juvenile rheumatoid arthritis
LCV	Leukocytoclastic vasculitis
LE	Lupus Erythematosus
LP	Lichen planus
LPP	Lichen planopilaris
LT	Lymphotoxin
LT-α	Lymphotoxin alpha
m	months
MTX	Methotrexate
MxA	Myxovirus resistance 1
NA	Not applicable
NK	Natural Killer
NMSC	Non melanoma skin cancer
N. resolved	Number resolved
NS	Non Stated
OLP	Oral lichen planus
OR	Odds ratio
pDCs	plasmacytoid dendritic cells
PPP	Palmoplantar Pustulosis
PsA	Psoriatic arthritis
PsO	Psoriasis

PUVA	Psoralen plus Ultraviolett A
RA	Rheumatoid arthritis
RANKL	Receptor activator of NFκβ ligand
SAPHO	synovitis, acne, pustulosis, hyperostosis, osteitis
s.c.	Sub cutaneous
SJS	Stevens Johnson syndrome
SLE	Systemic Lupus Erythematosus
SpA	Spondyloarthropathy
TEN	Toxic epidermal necrolysis
TNF-α	Tumor necrosis factor alpha
TNF-αRI	TNF-α class 1 receptor
TNF-α Tx c	TNF- α Treatment continued
TNF-α Tx d	TNF- α Treatment discontinued
TNF-γ	TNF gamma
Trail	TNF-related apoptosis inducing ligand
Tx	Therapeutics
UC	Ulcerative colitis
USA	United States of America
UVA	Ultraviolett A
UVB	Ultraviolet B
VZV	Varizella zoster virus
w	weeks
y	years

Summary

The introduction of tumor necrosis factor alpha (TNF-α) inhibitors in the treatment of Crohn's disease (CD) and rheumatoid arthritis (RA) nearly 15 years ago opened till then unknown therapeutic options in the treatment of chronic inflammatory immune-mediated diseases. Besides RA and CD, TNF-α has been shown to be dysregulated in psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and ulcerative colitis (UC). The pathogenesis of the aforementioned diseases comprises genetic, immunological and environmental factors. By targeting TNF-α, a key cytokine in the pathogenesis of the aforementioned diseases, it has been possible to block the inflammatory cascade in these diseases at an essential point in their pathogenesis. Today TNF-α inhibitors (comprising adalimumab, certolizumab, etanercept, golimumab and infliximab) are a mainstay in the treatment of those diseases and have been proven to be a very efficient and safe treatment option. However, adverse events due to TNF-α inhibitors have also been noted. Over the last years a plethora of cutaneous side effects has been reported. Out of these numerous side effects three of the most interesting are psoriasis, alopecia and lichen planus, which will be reviewed in detail in this work. As TNF-α inhibitors have been used more commonly over recent years in patients suffering from chronic inflammatory immune-mediated diseases, it appears to be of utmost importance for physicians to be aware of these cutaneous adverse events and to treat them accordingly.

Zusammenfassung

Mit der Einführung von TNF-α Inhibitoren zur Therapie des Morbus Crohn und der rheumatoiden Arthritis vor 15 Jahren, haben sich bisher unbekannte Therapieoptionen zur Behandlung chronisch entzündlicher immunmediierter Erkrankungen eröffnet. Neben den beiden gennannten Erkrankungen spielt eine Dysregulation von TNF-α in der Pathogenese der Psoriasis, der Psoriasisarthritis, der ankylosierenden Spondylitis und der Colitis ulcerosa eine bedeutende Rolle. Die Pathogenese dieser Erkrankungen umfasst neben genetischen und immunologischen Faktoren auch Umweltfaktoren. Durch die Blockade von TNF-α, einem wichtigen Zytokin in der Pathogenese der oben erwähnten Erkrankungen, wurde es möglich die Entzündungskaskade an einem wichtigen Punkt in der Pathogenese dieser Erkrankungen zu beeinflußen. Heutzutage sind TNF-α Inhibitoren (Adalimumab, Certolizumab, Etanercept, Golimumab und Infliximab) sowohl eine sichere als auch eine effiziente, wichtige Therapieoption zur Behandlung der oben genannten Erkrankungen. Trotz alledem wurden auch bei diesen Medikamenten Nebenwirkungen beobachtet, wobei in den letzten Jahren eine Vielzahl unterschiedlicher kutaner Nebenwirkungen registriert werden konnte. Aus dieser Vielzahl werden in der vorliegenden Arbeit die folgenden drei näher beleuchtet werden: Psoriasis, Alopezie und Lichen planus. Da TNF-α Inhibitoren in den letzten Jahren immer häufiger zur Therapie chronisch entzündlicher immunmediierter Erkrankungen verwendet wurden, erscheint es von großer Bedeutung, dass die behandelten Ärzte/Ärztinnen über die möglichen kutanen Nebenwirkungen Bescheid wissen und diese auch entsprechend behandeln können.

1 Introduction

The introduction of tumor necrosis factor alpha (TNF-α) inhibitors in the treatment of Crohn's disease (CD) and rheumatoid arthritis (RA) nearly 15 years ago opened till then unknown therapeutic options in the treatment of chronic inflammatory immune mediated diseases.[1, 2, 3] Besides RA and CD, TNF-α has been showing to be dysregulated in psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and ulcerative colitis (UC).[4, 5, 6, 7] The pathogenesis of the diseases, which were mentioned before, comprises genetic, environmental and immunological factors.[4, 5, 6] By targeting TNF-α, a key cytokine in the pathogenesis of the aforementioned diseases, it has been possible to block the inflammatory cascade in these diseases at an essential point in their pathogenesis[8, 9, 10, 11] Today TNF-α inhibitors are a mainstay in the treatment of these diseases and they have been proven to be a very efficient and safe treatment option.[8, 9, 10, 11, 12] However, even with these drugs adverse events due to these TNF-α inhibitors have been noted. A phletora of cutaneous side effects has been reported over the last years.

The objective of the present thesis was to review cutaneous side effects in patients treated with TNF-α inhibitors. Therefore, a MEDLINE search of cutaneous side effects in patients with TNF-α inhibitors was performed. Search terms used were TNF-α inhibitor, adalimumab, certolizumab, etanercept, golimumab infliximab, Crohn’s disease, inflammatory bowel disease, psoriasis, rheumatoid arthritis, psoriatic arthritis, cutaneous side effects, alopecia, lichen planus, injection side reactions, infusion reaction, lupus-like dermatitis, infections, basal cell carcinoma, squamous cell carcinoma and melanoma.

1.1 Tumor Necrosis Factor- α

Tumor necrosis factor alpha (TNF-α) is a pleiotropic proinflammatory cytokine.[13] In the last 10-15 years researchers have established the crucial role of TNF-α in immune-mediated diseases. TNF-α over-expression has been found in the skin of psoriasis patients, in the synovium of joints affected by PsA, RA and AS, as well as in the intestinal tissues from patients suffering from IBD. Furthermore elevated serum levels of TNF-α have been detected in these patients.[4, 5, 6, 7] TNF-α belongs to the so-called TNF superfamily which also comprises other mediators like lymphotoxin (LT), CD 40 ligand (CD40L), Fas ligand (FasL) as well as TNF-related apoptosis inducing ligand (TRAIL) and receptor activator of nuclear factor NFκβ ligand (RANKL).[13] The following TNF superfamily members possess proinflammatory properties: TNF-α, LT-α, FasL, CD30 ligand primarily by inducing NFκβ, whereas most members of the TNF-superfamily are mainly involved in apoptosis and cell regulation.[13]

As I will primarily focus on the role of TNF-α in immune mediated inflammatory diseases or to put it more straight on the inhibition of TNF-α in immune-mediated inflammatory diseases I will not describe the different properties of TNF-α like its role in apoptosis or in the alteration of energy and substrate metabolism. TNF-α is produced by a great variety of cells. Among these cells are B and T-cells, neutrophils, mast cells, dentritic cells, natural killer (NK) cells as well as many non-immune cells.[14, 13] TNF-α is considered a particularly important cytokine in the complex cytokine network in immune mediated inflammatory diseases. It has shown to be a potent inducer of inflammatory responses as well as key regulator in innate immunity.[13, 15] It also plays a crucial role in the regulation of the Th1 immune response by amplifying it through the up-regulation of IL-12 and interleukin (IL)-18 and therefore leading to an increased Interferon (IFN)-γ production and $CD4^+$ T-cell activation.[13] This finally results in an increase of TNF-α production in macrophages and an activation of the inflammatory response.[13]

1.2 TNF-α Inhibitors

TNF-α inhibitors have become a mainstay in the treatment of immune mediated inflammatory diseases with more than 2,006,000 patients treated worldwide.[16]

The following TNF-α-antagonists are currently commercially available in the European Union and the USA: adalimumab, certolizumab, etanercept, golimumab, and infliximab. Their EMEA and FDA approved indications as well as their trade names are given in tables 1. Adalimumab, golimumab, and infliximab are IgG1 antibodies[15, 17], whereas certolizumab is a Fab[1] fragment of a monoclonal IgG1 antibody.[15] Etanercept is a fully human dimeric fusion protein composed of the Fc portion of IgG-1 and a TNF-α type II receptor.[15, 17] Except for infliximab, which is administered intravenously all other TNF-α inhibitors are administered subcutaneously.[15, 17] Their application frequency ranges from two times a week (etanercept) to every 6-8 weeks (infliximab).[15]

In comparison to adalimumab, infliximab and rituximab; efalizumab and golizumab are relative new TNF-α inhibitors.

TNF-alfa blocker approved in the US

trade name	**active ingredient**	**application**	**mechanism of action**	**indication**
Remicade	Infliximab	infusion	monoclonal antibody	PsO,CD,AS,PsA,RA,UC
Enbrel	Etanercept	s.c.	fusion protein	CD,AS,PsA,CPP,JIA,RA,UC
Humira	Adalimumab	s.c.	monoclonal antibody	CD,AS,PsA,CPP,JIA,RA,UC
Cimzia	Certolizumab pegol	s.c.	monoclonal antibody	CD
Simponi	Golimumab	s.c.	monoclonal antibody	PsA,AS,RA

TNF alfa blocker approved in Europe

trade name	active ingredient	application	mechanism of action	indication
Humira	Adalimumab	s.c.	monoclonal antibody	CD,AS,PsA,RA
Enbrel	Etanercept	s.c.	fusion protein	PsO,RA
Remicade	Infliximab	i.v.	monoclonal antibody	PsO,CD,AS,PsA
Cimzia	Certolizumab pegol	s.c.	monoclonal antibody	RA
Simponi	Golimumab	s.c.	monoclonal antibody	AS,PsA,RA

Table 1: Approved TNF- *α* inhibitors in the US and Europe[18, 19]

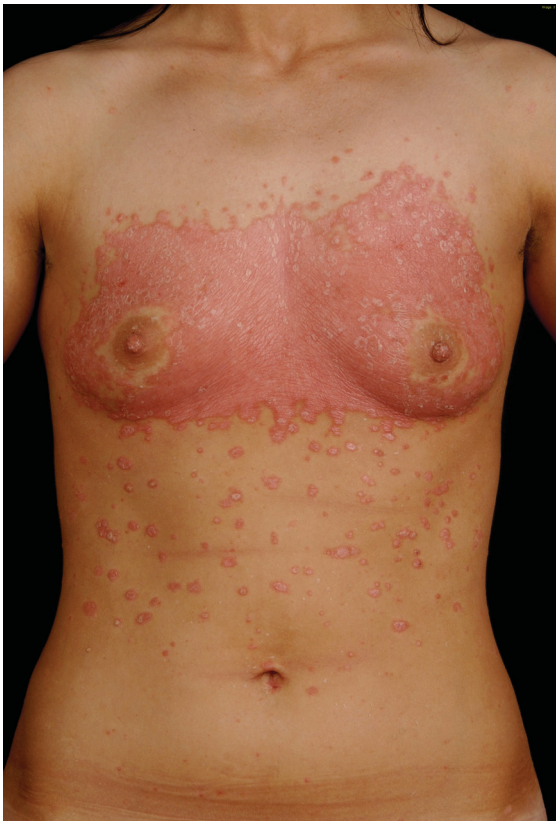

Figure 1: Psoriasis before therapy with Adalimumab

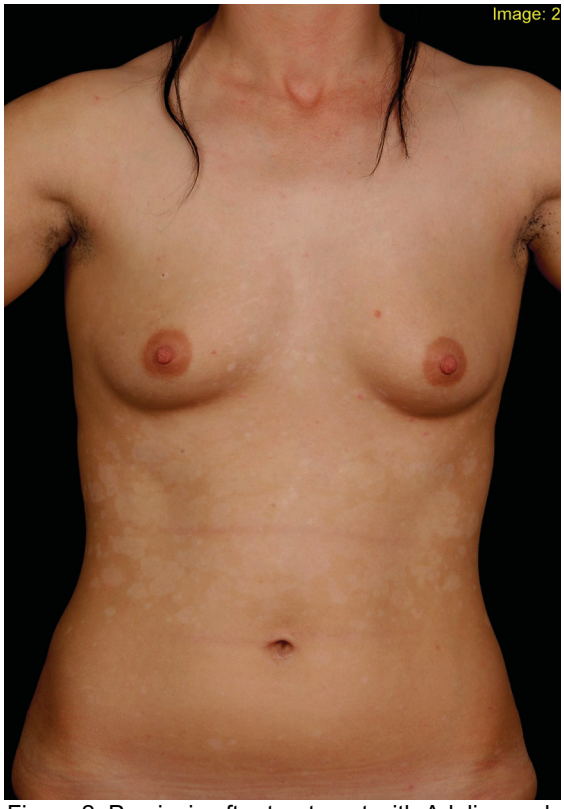

Figure 2: Psoriasis after treatment with Adalimumab

2 Underlaying diseases

2.1 Psoriasis and psoriatic arthritis

Psoriasis is a chronic inflammatory disease affecting 2-3% of the general population in the Western hemisphere.[6, 8] As in RA, the disease is considered to have a multifactorial and complex pathogenesis with a strong genetic background[6, 8] Clinically psoriasis presents as a heterogeneous disease. Chronic plaque psoriasis is the most common type (85-90% of all cases), rarer forms comprise guttate psoriasis, erythrodermatic, inverse, palmoplantar and pustular (generalized and localized) psoriasis.[6, 8, 20]

It is not contagious and caused by a hyperproliferation of the epidermis. Due to psoriasis, the growth cycle of the skin is accelerated. New cells build up too quickly, which lead to scaly lesions on the skin. Lesions appear all over the body, however they affect especially knees, trunk and ellbows. Patients suffer from itchy, red skin, which is also thick and dry[21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]

Psoriasis may not only involve the skin, but may also affect the joints. Psoriatic arthritis (PsA) has also been found to be quite heterogeneous ranging from peripheral joint involvement to sacroiliitis and psoriatic spondylarthropathies. Recently it has been shown that psoriatic arthritis affects up to 20% of the psoriasis patients in Central Europe.[37, 38] Besides skin and joint manifestations the nails and entheses can also be affected by psoriasis.[8, 20] Psoriasis is also associated with a great variety of comorbidities, such as: cardiovascular disease, metabolic syndrome, arterial hypertension and obesity.[39] Due to the chronicity of the disease the quality of life has been shown to be impaired.[40]

In psoriasis the following risk factors and triggers are known: a positive family history of psoriasis, infections, stress, obesity, alcohol, injuries to the skin, smoking and various drugs such as lithium and β-blockers.[41]

Besides IL12, IL 23 and IL 17, TNF-α is a key cytokine in the immunopathogenesis of psoriasis and psoriatic arthritis. By blocking TNF-α highly efficient and successful treatment of psoriasis is possible.[8, 42, 43, 44, 45, 46, 47]

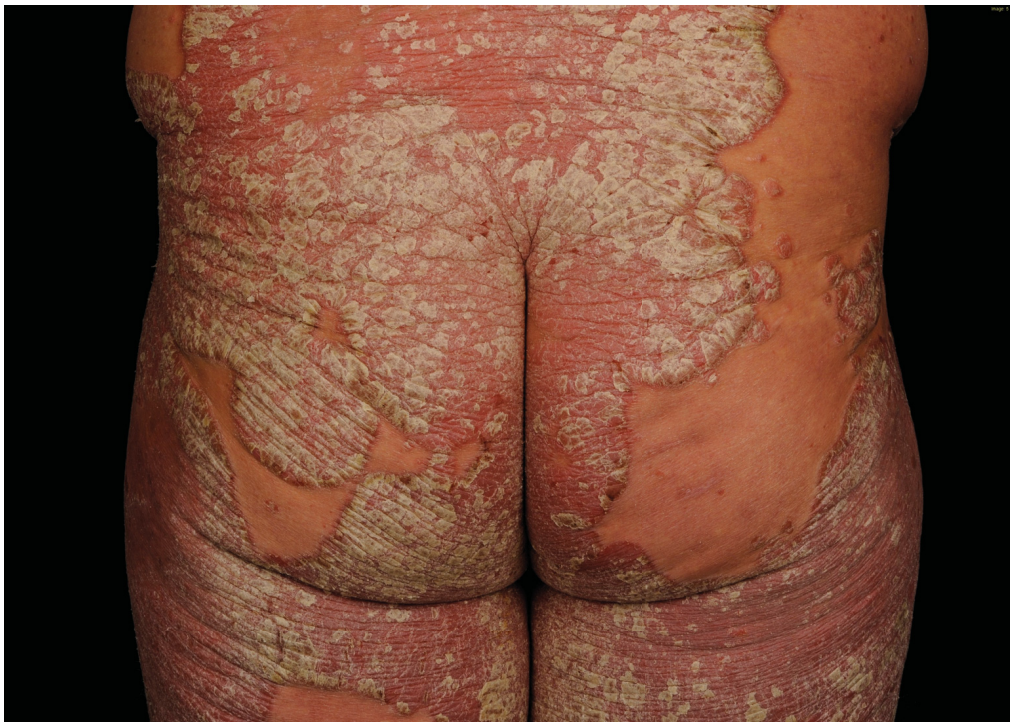

Figure 3: Chronic plaque type psoriasis

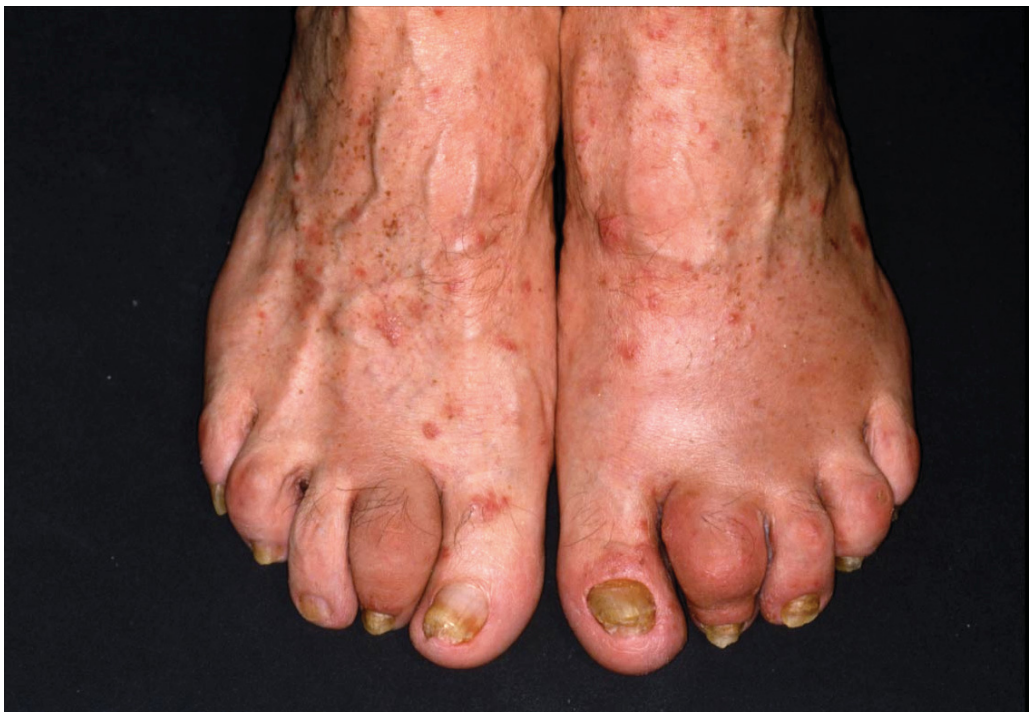

Figure 4: Dactylitis of both second toes in a psoriatic patient

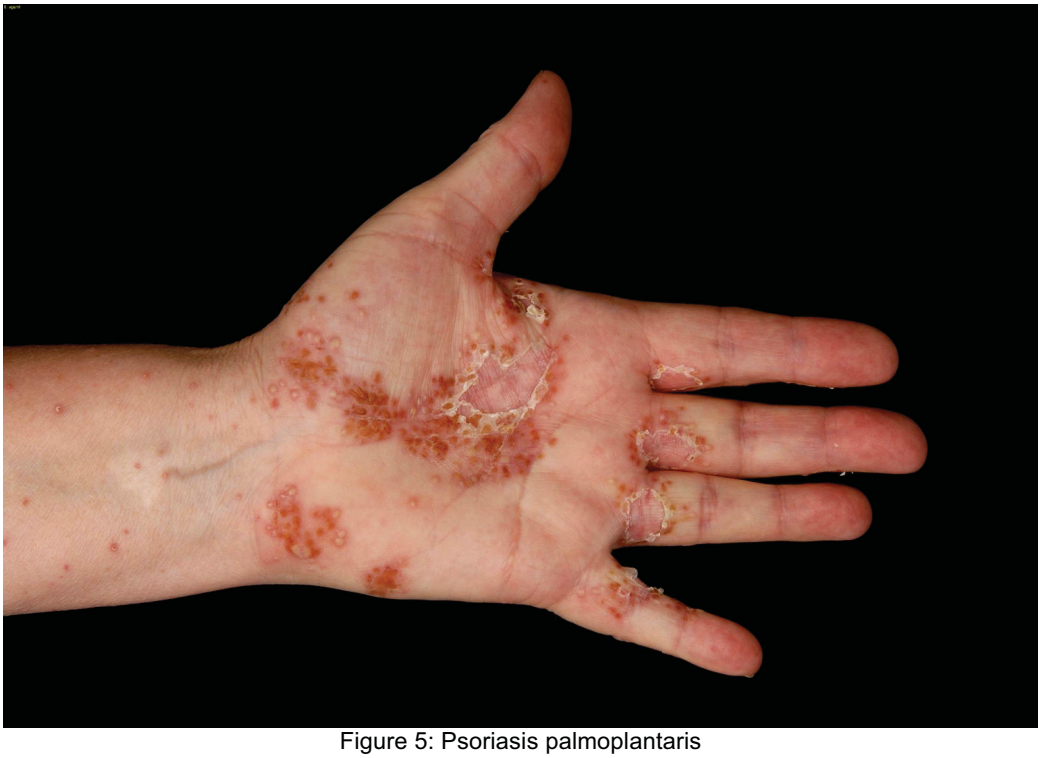

Figure 5: Psoriasis palmoplantaris

2.2 Rheumatoid Arthritis

RA is a chronic inflammatory disease affecting 0.5-1 % of the population.[48, 49, 109] RA is characterized by mainly inflammation of the synovial tissues resulting in joint destruction and therefore leading to functional disability and significant impairment of quality of life. Systemic features of RA comprise the cardiovascular, pulmonary, and the skeletal system".[48] Women are considerably more often affected than men.[49] Patients with a RA have a higher cardiovascular mortality, and a greater risk of infection compared to the general population.[48] It has been shown that the incidence of hematopoietic and pulmonary cancer is increased in comparison to the general population.[49] It has been further demonstrated that the risk of lymphomas in RA patients clearly is increased and related to the degree of inflammation.[50, 49]

Chakravarty et al could show that patients with RA have an increased risk for non-melanoma skin cancer (NMSC) and melanoma.[51]

Cutaneous manifestations of RA include palmar erythema, rheumatoid nodules (20-30% of RA patients), rheumatoid vasculitis and granulomatous dermatitis.[48, 52,

[53] The pathogenesis of RA is multifactorial comprising genetic, environmental and immunological factors.[5, 49]

Besides IL-1α; IL-1β, IL 6; IL 18 and IL-33 TNF-α plays a central role in the pathogenesis of RA. Other cytokines [5] like IL-17 and IL-17 receptor are currently under investigation as new targets in the treatment of RA. The TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab have been proven to be highly efficient in the treatment of RA by reducing RA symptoms, and to significantly improve quality of life of RA patients.[9, 54, 109]

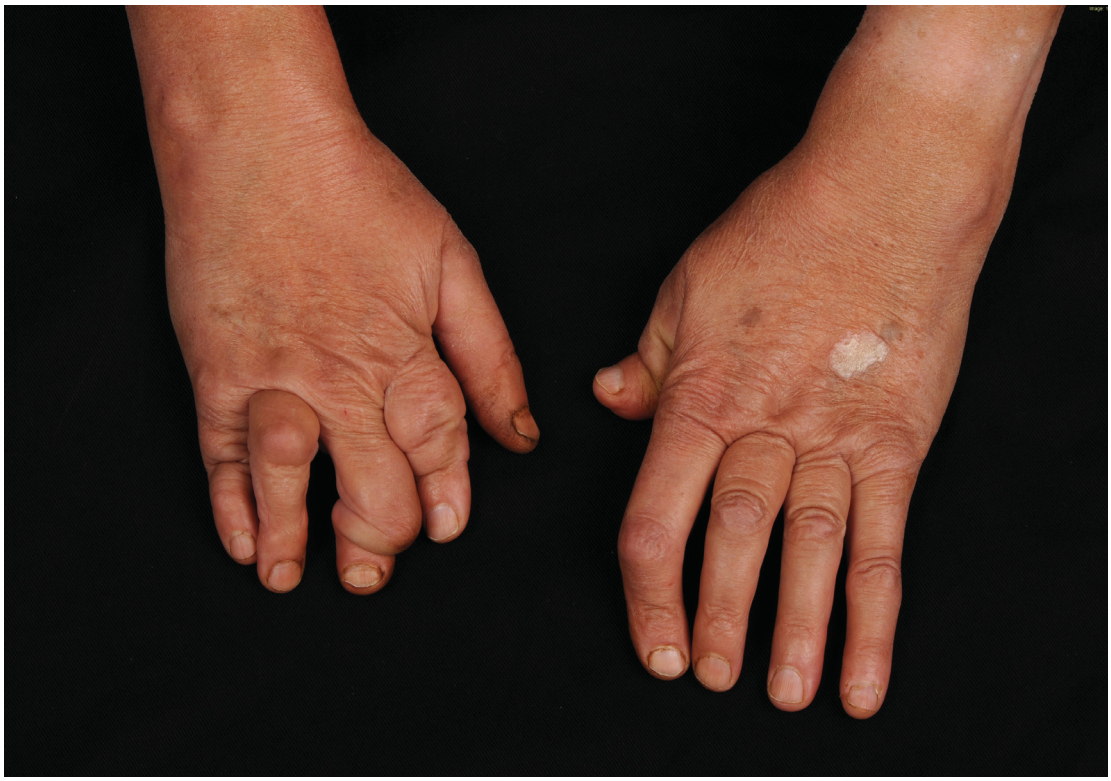

Figure 6: Deformities of the digits in patients suffering from rheumatoid arthritis

2.3 Ankylosing spondylitis

Ankylosing spondylitis belongs to the so-called seronegative spondylarthropathies, which also comprise PsA, arthritis related to inflammatory bowel disease (IBD), reactive arthritis and a subgroup of juvenile idiopathic arthritis.[7, 55] The prevalence of AS in Central Europe ranges from 0.55-0.94%.[55, 56, 57, 58]

AS patients are suffering from chronic back pain, associated enthesopathy, and peripheral arthritis.[55] Interestingly, Roussou et al could show that women suffer more frequently from cervical and thoracic spine involvement and less from

ankylosis. Genetically there is a strong association to HLA B27 (80-90% of AS patients).[7, 55, 59]

Of particular interest a definite association has been found in genome wide association scans (GWAS) with endoplamatic reticulum aminopeptidase (ERAP 1) and interleukin-23 receptor.[60, 61] It should be noted that CD and psoriasis show although a highly significant genetic association with IL-23R.[62, 63] Recently a significant genetic association between ERAP 1 and psoriasis has been demonstrated by a GWAS.[64] In the literature the male: female ratio in AS varies between 2:1 to 9:1.[55] As has also been shown for RA and psoriasis, cardiovascular morbitity is more common in AS patients than in the general population [65, 66, 67] TNF blockade has been proven to be highly effective in AS.[7, 55]

2.4 Inflammatory bowel disease (IBD)

Crohn's disease (CD) and ulcerative colitis (UC) are the main types of idiopathic inflammatory bowel disease.[4] Both are chronic diseases sharing a complex pathogenesis involving pathologic interaction of the immune system with commensal enteric bacteria in genetically susceptible individuals.[4, 68] IBD affects approximately 1.4 million patients in the USA and approximately 2.2 million patients in Europe.[68] Whereas CD involves the ileum and the colon uninterruptedly in most patients (but can affect any region of the gastrointestinal tract as well) UC tends to affect and the rectum uninterrupted.[4] A further difference between the two entities can be seen concerning the involvement of the gastrointestinal tissues: in CD the inflammation is transmural, whereas in UC the inflammatory changes are confined to the mucosa.[4] According to Engel and al[68] there is a slight female predominance in CD. In contrast UC men are affected predominately.[68] Extraintestinal manifestations are common in IBD. Cutaneous manifestations of IBD are erythema nodosum, and pyoderma gangraenosum. Interestingly the prevalence of psoriasis in CD patients is significantly higher than in the general population, accounting for around 9% of all CD patients.[69] The cytokine pattern in IBD displays elevated levels of TNF-α IL-6, IL-8, IL-12, IL-23 and IL-17.[4, 68, 69, 70] CD has been one of the first diseases were TNF-α inhibitors have been introduced successfully.[1] Over the last decade TNF-α inhibitors (adalimumab, certolizumab and infliximab) have become a mainstay in the treatment of IBD, which until now

has been proven to be efficient and quite safe.[10, 11] Interestingly, in contrast to the monoclonal TNF-α antibodies (adalimumab, certolizumab and infliximab) etanercept, a fully human dimeric fusion protein, did show only little efficiency in the treatment of CD.[71]

3 Cutaneous side effects

Cutaneous side effects concerning patients treated with TNF-α inhibitors have been increasingly reported over the last years. These side effects comprise a wide range of dermatological manifestations like psoriasis, infusion reactions, injection site reactions, granuloma annulare, alopecia, eczema, autoimmune skin disorders (e.g. lupus like dermatitis), lichen planus, vasculitis, erythema multiforme/Stevens Johnson syndrome, toxic epidermal necrosis, cutaneous infections and cutaneous malignancies (e.g. basal cell carcinoma, squamous cell carcinoma, melanoma, and cutaneous lymphomas). [11, 72, 73, 74, 75, 76, 77, 350, 365] Whereas infusion reactions are restricted to infliximab, the only TNF-α inhibitors commercially available, which is administered intravenously, the other side effects have been noted with at least one of the available TNF-α inhibitor approved by the FDA and EMEA. Moustou et al reported in their review article[350] the frequency and strengths of the association of the adverse events with TNF-α therapy. The results are given in Table 2.
As a detailed review of all the reported cutaneous side effects is beyond the scope of this work the focus in the following section will be laid in more detail on three particular interesting cutaneous side effects: psoriasis and psoriasiform reactions, lichen planus as well as alopecia.

Cutaneous adverse event	**Drug**	**Clinical outcome**	**Estimated frequenzy**	**Strenght of association**	**Reference**
Non-tuberculosis mycobacterial skin infections	INF	Resolution after appropriate Tx	Extremely rare	Moderate/strong	78, 79, 80

Fungal infection	INF, Etan, ADA	Resolution with appropriate Tx	<8%	strong	[81]
Infusion reactions Acute	INF	Resolution with reduction of infusion rate, systemic administration of antihistamines and/or corticosteroids.Discontinuation of Tx in<1% if severe reactions occur	<5% of infusions	Definite	[350]
Infusion reactions Delayed	INF	Resolution and prevention of relapses with concomitant administration of systemic immunosuppressives(MTX, Aza). Prevention with regular infusions during maintenance Tx	<1% of infusions	Definite	[350]
Injection site reactions	Etan ADA	Self-limited. Decrease in frequenzy with continuation of Tx. „Recall reactions may occur	≈10% of patients	Definite	[350]
Papulopustular eruptions Psoriasis, psoriasiform eruptions	INF, Etan, ADA	Resolution with either topical Tx, UVB or PUVA, or Tx discontinuation	<1% of patients	Strong	[81, 82, 83, 84]
Eczema	INF, Etan, ADA	Resolution with either topical Tx, or discontinuation	Unknown	Moderate/strong	[81, 83]
Lichenoid drug reactions	INF, Etan, ADA	Resolution with discontinuation and/or systemic corticosteroids	Unknown	Moderate (limited experience)	[85, 86]
Autoummune skin disorders LE (systemic, subacute,	INF, Etan, ADA	Resolution with discontination and/or systemic corticosteroids, anti-malarial agents, or immunosuppressive agents	<0.5% of patients	Strong	[76, 87]

discoid types)					
Vasculitis	INF, Etan, ADA	Resolution with discontinuation and/or systemic corticosteroids, immunosuppressive agents	<0.5% of patients	Strong	76, 81, 88
Granulomatous reactions Granuloma annulare	INF, Etan, ADA	Resolution with topical corticosteroids; anti-TNF discontinuation was necessary in only 2 patients out of 9	<5% of patients	Poor/moderate	89
Cutaneous infections Bacterial infections (skind and soft tissue)	INF, Etan, ADA	Resolution with appropriate Tx	<5% of patients	Strong	78, 81, 83, 90, 91, 92, 93
Herpesvirus infections (HSV 1,2-VZV)	INF, Etan, ADA	Resolution with appropriate Tx	1%- 2% of patients	Strong	81, 83, 91, 93
Cutaneous malignant neoplasms Lymphomas CTCL	INF, Etan	Improvement after Tx discontinuation, death		Poor	94, 95, 96, 97, 98
Lymphomatoid papulosis-like eruption	ADA	Spontaneous resolution; developemnt of non-Hodgkin ALCL 2 years later	1 event/289 RA patients	Poor	81
Systemic ALCL with cutaneous involvement Sézary syndrome	INF	Partial remission with infliximab discontinuation and MTX Tx		Poor	95, 99
NMSC	INF, Etan, ADA	Excision		Poor	51, 81, 100, 101, 102, 103, 104

Melanoma	Etan, ADA	Tx with isolated limb chemotherapy in one patient, lymph node dissection		Poor	105, 106
Kerathocanthom Benign cutaneous neoplasms	INF	Discontination of Tx		Poor	102
Eruptive nevomelanocytic nevi	INF, Etan			Poor	107

Table 2: Cutaneous side effects modified according to Moustou et al.

3.1 Psoriasis (and psoriasiform eruptions)

As has been discussed before TNF-α inhibitors have proved to be very efficient drugs in the treatment of moderate to severe psoriasis and in PsA.[8, 108, 109, 110, 111, 112, 113, 114, 115] Paradoxically, in some cases TNF-α inhibitors were found to induce psoriasis. The first cases were reported as early as in 2003.[116, 400] Since then TNF-α induced psoriasis has been described in many case reports and some case series in the literature.[24, 25, 80, 81, 82 85, 108, 109, 110, 111, 113, 114, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 212, 214 222, 285, 286, 292, 400]

Searching the literature we could identify 413 cases (265 females, 125 males and in 23 patients the gender has not been applicable; male to female ratio 1: 2.1) were identified. The patients' age ranged from 7 to 83 years (mean 43.6 years). Fifteen patients (8 females and 7 males; aged 7-17 years; mean13.2 years) were children and adolescents, respectively. Patients receiving TNF-α inhibitors were suffering from CD (151 patients, 36.5%), RA (127 patients, 30.7%), AS (42 patients, 10.2%), combined AS and CD (5 patients, 1.2%), psoriasis (31 patients, 7.5%), UC (25 patients, 6.5%), non specified inflammatory bowel disease (9 patients, 2.2%). The remaining 5.2% of patients were suffering from a broad variety of diseases like Behçet's disease (BD), juvenile idiopathic arthritis (JIA),

SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, Shulman syndrome, tumor necrosis factor receptor associated periodic fever (TRAPS), uveitis, vitiligo and not nearer specified arthritis. Male to female ratio was found to be 1.2:1 in patients bot hwith psoriasis and in patients with AS, 1:4.8 in RA patients and 1:1.9 in patients suffering from CD. 236 patients had been treated with infliximab (57.1%), 103 with a adalimumab (24.9%), 64 with etanercept (15.5%), and 6 with certolizumab (1.5%), respectively In 4 patients (1%) the TNF-α inhibitors administered were not specified by the authors.[123, 196]

Personal history of psoriasis was negative in 73.6%, positive in 12.8% and not reported in 13.6%, whereas family history psoriasis was negative in 54.2%, positive in 37.3% and not available in 38.5%.

The clinical spectrum ranged from plaque type psoriasis (27.1%), palmoplantar pustular psoriasis (21.8%), psoriasiform eruptions (18.1%) to generalized pustular psoriasis, inverse and guttate psoriasis, as well as combined types of the aforementioned psoriasis phenotypes. When considering all patients suffering from palmoplantar pustular psoriasis (PPP) [e.g. patients with PPP only (90 patients) and those suffering from PPP in combination with a different phenotype (74 patients)] 39.7% of all patients displayed this phenotype. Interestingly, psoriatic nail disease was only found in a minority of patients (2.7%; 7 females, 2 males and in two patients the sex was not reported). Six patients affected by nail psoriasis were suffering from RA, four from IBD, and one from BD, respectively. Psoriatic nail changes comprised onycholysis, pitting, nail discolorations well as subungual hyperkeratosis.[109, 112, 115, 121, 134, 204, 313]

Treatment with TNF-α was continued in 149 patients (36.1%) with complete or partial improvement, in 133 patients (32.2%) TNF-α therapy was discontinued. In 69 patients (16.7%) therapy was switched from one TNF-α inhibitor to another one. In 57 patients (15%) no data were given concerning further TNF-α therapy. Furthermore in the majority of patients topical treatment with steroids and vitamin D preparations was initiated. Other modalities used for treating psoriasis comprised UVB 311 nm and PUVA therapy, methotrexate as well as cyclosporine A.

The incidence of TNF-α induced psoriasis has been estimated in a study by Harrisson et al to be 1.04 per 1.000 patients years among 9826 patients with TNF-α inhibitors compared to none in 2880 patients treated with DMARDs.“[84] However,

the true incidence is still unknown, mainly due to underreporting. Prevalence rates in the literature are ranging from 0.6-5.3%.[81, 83, 109, 112, 117, 129, 140, 144, 181, 205, 207, 303]
The pathogenesis of this paradoxical reaction is still not fully elucidated yet. It has been hypothesized that reducing circulating TNF-α levels might be associated with increased interferon-α levels and thus creating a cytokine imbalance. IFN-α is produced by plasmacytoid dentritic cells (pDCs) and leads to the activation and amplification of TNF-α producing T-cells.[6, 205, 206] INF-α also up-regulates the chemokine CXCR3, resulting in migration of activated T-cells into the skin.[23, 25, 224] PDCs have been shown to be present in the early psoriatic plaque as well as in normal skin of psoriasis patients.[6] In vitro experiments were able to show that inhibition of TNF-α leads to increased production of IFN-α by pDCs.[25] It has also been shown by several authors.[23, 160, 224] that anti-myxovirus resistance protein A (MxA), an adenosine triphosphatase selectively induced in response to IFN-α as well as IFN-β, was found in skin samples of TNF-α induced psoriasis. Seneschal et al also found increased expression of CXCL9, CXCR3 and Tia1 in psoriasiform lesions by using immunohistochemical staining, thus confirming a type I interferon signature in these lesions.[23] Furthermore, they noted an increase in $CD3^+$ T-cells and a double fold increase in the CD8/CD4 ratio in psoriasiform lesions compared to psoriatic controls not treated with TNF-α inhibitors.[23] Histopathology revealed a psoriasiform pattern with parakeratosis, hyperkeratosis and acanthosis. Interestingly, a focal lichenoid pattern characterized by a lymphocytic infiltrate in the upper dermis and epidermal basal cell damage was visible in some cases.[23] In one of their patients suffering from psoriatic arthritis the authors performed two biopsies, one from an original psoriatic plaque and one from a psoriasiform eruption. In contrast to the psoriasis lesion, the psoriasiform eruption displayed a psoriasiform pattern with spongiosis and a prominent perivascular mononuclear infiltrate.[23] Therefore, the authors concluded that TNF-α induced psoriasiform eruption has to be considered as an adverse drug reaction different to “true” psoriasis.[23] However, other authors did note that the psoriatic lesions were histologically indistinguishable from patients with idiopathic psoriasis.[23, 24, 74, 160, 191, 312]

Whereas plaque psoriasis is the most common type of idiopathic psoriasis accounting for 85-90% of all cases[8], PPP is found in up to 39.7% of all cases of TNF-α induced psoriasis. It has been hypothesized that this fact might be due to a

genetic predisposition in a certain subset of patients.[74, 82, 160, 204, 207] It is also noteworthy that in the majority of patients a personal history of psoriasis (73.6%) as well as the family history of psoriasis (54.2%) was negative. However, one has to consider that a personal history and/or a family history of psoriasis wer not available in 13.6% and 38.5% of patients, respectively. Some authors[207] speculated that in patients with RA misdiagnosis of psoriasis could be a cause since psoriatic PsA sine psoriasis might precede psoriatic skin manifestations.
The decision concerning continuation of TNF-α treatment in patients suffering from TNF-α- induced psoriasis depends on several factors: first of all on the response of the underlying disease to the TNF-α inhibitors, second on the severity of the psoriasis and as third point on the available treatment alternatives for the underlying disease.[74, 82, 160] Effective topical treatment or adding a second DMARD might be helpful when continuing TNF-α therapy. Switching to another TNF-α inhibitor has also been proven to be a useful strategy in some patients. At the moment no tests are available to identity patients which will profit from the aforementioned therapeutic strategies. Probably pharmacogenetic testing might provide a useful option in the future. [208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224]

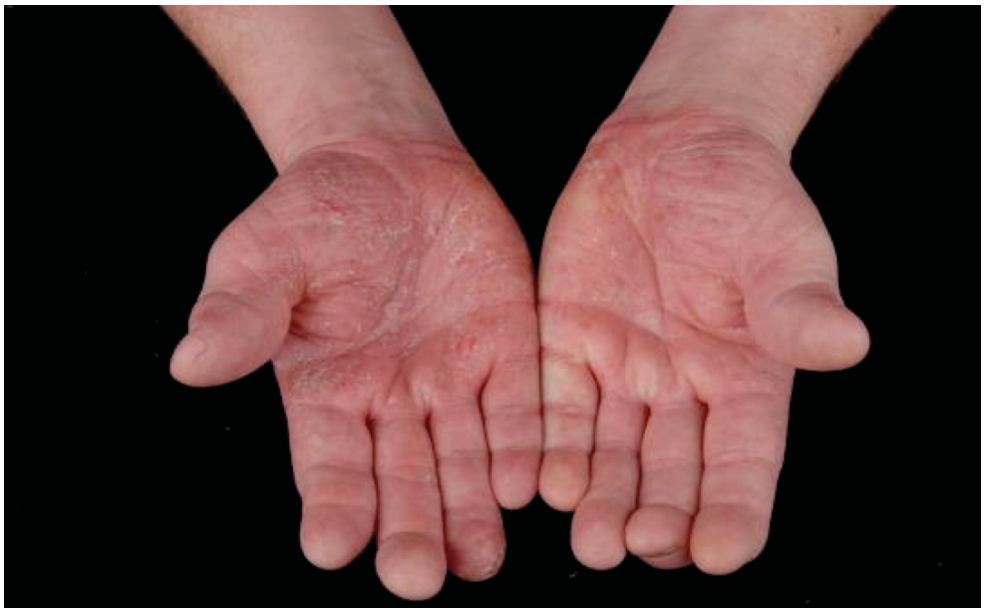

Figure 7: Psoriasis palmoplantaris induced by infliximab in a patient suffering from PsA

3.2 Lichenoid reactions and lichen planus like eruptions

Lichen planus (LP) nowadays is considered a T-cell mediated autoimmune disease of unknown etiology.[225, 226] The estimated prevalence in the Western hemisphere is around 1% .[226] T-cells ($CD4^+$ and $CD8^+$ T cells) play a major role in the pathogenesis of LP.[225, 226] These T cells have been shown to release a variety of cytokines (including IFN-γ and TNF-α).[225, 226] Besides topical treatments (e.g. topical steroids, topical calcineurin inhibitors as well as topical ciclosporin), systemic treatment options comprise steroids, retinoids and phototherapy.[225, 226, 227] Recently, biologics (infliximab, etanercept and adalimumab) have been successfully introduced in the treatment of severe oral lichen planus (OLP) in a small series of patients.[225, 227] However, it has also been observed that in patients treated with TNF-α antagonists LP-like lesions or lichenoid reactions may occur. According to the English speaking literature, twenty-two patients (12 males, 9 females, and in one patient the gender was not reported) developed lichen planus like eruptions under anti-TNF-α treatment [81, 85, 165, 212, 213, 214, 216, 217, 218, 219, 220 222, 228, 229, 230, 231, 232, 315] Patents were aged between 8- 71 years (mean age 50.4 years). Ten patients had been treated with infliximab, 7 with etanercept, 3 with adalimumab, and one each with certolizumab pegol and lenercept, respectively. The onset of lichenoid eruptions ranged from a few hours (14 hours) to 172 weeks (mean 31.1 weeks, median 7-8 weeks]. Nine patients (40.9%) received TNF-α inhibitors for treating psoriasis, 8 patients for RA (36.3%, including one patient treated for toxic epidermal necrolysis with etanercept), 2 patients for CD (9.1%) and one patient each for AS, Sjögren's syndrome as well as JIA in combination with CD (4.5% each), respectively. The oral mucosa was affected by lichen planus like lesions in 6 patients (27.7%), the trunk and the extremities in 16 patients (72.7%). In 9.1% (2 patients) LP affected the oral mucosa as well as the trunk and the extremities. In one patient (4.5%) only oral and genital mucosa was found to be affected by the disease. Lichen planus associated nail changes (pterygium and nail fissuring) were visible in one patient (4.5%). Lichen planopilaris (LPP) leading to irreversible hair loss was noted in three patients (13.5%).[218, 222, 223] The lichenoid lesions on the trunk and the extremities varied clinically from classic LP with flat topped violaceous papules and plaques to generalized macular or papular exanthemas. One should also note that these lichen like eruptions were also noticed on the palms and in the gluteal region, which are not typically affected in

classic LP. Oral lesions showed also a certain clinical variability ranging from white reticular plaques to erosive lesion. Histology displayed lichenoid inferface dermatitis in the majority of patients.[212, 214, 219, 228, 229, 232] In patients suffering from LPP the histology was proven to be consistent with the diagnosis of LPP.[218, 222, 231] Interestingly, lichenoid interface dermatitis has also been found in some of the patients presenting clinically with psoriasiform eruptions[23, 118] which has been discussed in an aforementioned section of this work.

Clinical outcomes were as follows: lichenoid eruptions completely resolved in 13 patients, 6 patients had partial improvement and in 3 patients no improvement occurred. The pathogenesis of anti-TNF-α induced lichenoid eruption has not yet been elucidated. Some authors speculated that cytokine imbalances concerning TNF-α and IFN-α like in anti-TNF-α induced psoriasis might be the cause.[229] Others have suggested that inhibiting TNF-α production by keratinocytes or apoptosis of T cells expressing TNF-αRI might be causative.[228]

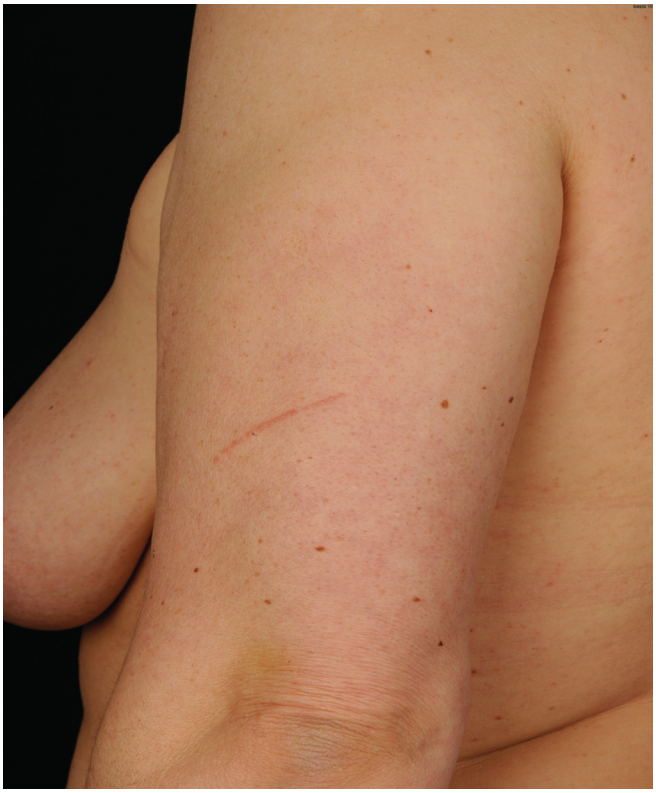

Figure 8: Koebner phenomen in a patient with adalimumab induced lichen planus

4 Further TNF-α induced diseases

In the following sections of my thesis I will focus on diseases that are thought to be common or are rare but are deemed to be of special interest for the clinician.

4.1 Eczema and atopic dermatitis

Atopic dermatitis is a common disease worldwide.[233, 234, 235, 236, 352, 354] It affects approximately 20% of all children and around 3% of adults.[352, 354] It has long thought to be primarily a Th2 mediated disease, whereas RA and psoriasis are considered to be Th1 mediated diseases.[8, 352, 48] Interestingly, eczema and atopic dermatitis might occur as cutaneous side effects of TNF-α inhibitors in patients with psoriasis, IBD or RA. Most commonly adalimumab and infliximab were considered to be the causative culprits, however also certolizumab and etanercept have been used in some cases[77, 81, 83, 204, 237, 238, 239]

Flendrie et al reported 20 RA patients suffering from eczema out of 289 RA patients under anti-TNF-α therapy with adalimumab and infliximab.[81] Eczematiform lesions were found in 23 patients in a retrospective multicenter study in patients suffering from IBD.[204] Adalimumab, certolizumab and infliximab had been administered in these patients. The median time to onset of symptoms was 11 months (range 1-25 months). In the majority of cases topical treatment using steroids and/or calcineurin inhibitors proved to be sufficient to control the disease.[81, 204] However, in some patients only discontinuation of anti-TNF-α therapy led to improvement of the cutaneous side effects.[81, 204, 239]

4.2 Drug-induced lupus erythematosus

Lupus erythematosus (LE) is a heterogenous and potentially life-threatening autoimmune disease. [240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255] Pathogenetically LE displays increased activity of the innate and adaptive immune system.[255] Disturbed cytokine balances have been found in LE patients, e.g. elevated levels of B-cell activating factor (BAFF), IL-6, IFN-α and TNF-α.[255, 256, 257, 258] In patients with lupus nephritis as well as lupus arthritis short term TNF-α blockade appears to be of some use[255, 259], whereas long term therapy seems to be associated with life-threatening events.[255] However, TNF-α inhibitors have also

been shown to induce LE or lupus-like dermatitis.[76, 254, 260] Despite the fact that patients under anti-TNF-α treatment may develop antinuclear antibodies (ANA)[244] the induction of lupus-like dermatitis or LE seems to be infrequent. The prevalence of lupus-like syndrome has been estimated to range from 0.5-1.19%.[87, 254, 256, 350] All TNF-α antagonists (adalimumab, certolizumab, etanercept, golimumab and infliximab) have been implicated in the induction of lupus-like dermatitis.[254, 261] In the majority of patients only the skin is involved. However, involvement of other organs has also been reported.[247, 254]

Cutaneous manifestations ranged from malar rash, urticarial rash, purpura, pruritic erythematous papules and plaques, increased photosensitivity to oral ulcers. Interestingly, not all patients do fulfil more than 4 criteria of the American College of Rheumatology classification. [75, 254, 350] Discontinuing anti-TNF-α treatment combined with topical therapy led to remission of lupus like dermatitis in the majority of patients. Only in a minority of patients anti-malarials and immunsuppressants are needed for treatment of lupus-like dermatitis and drug induced LE.[76, 350]

In patients with systemic involvement of LE discontinuation is deemed mandatory.[76]

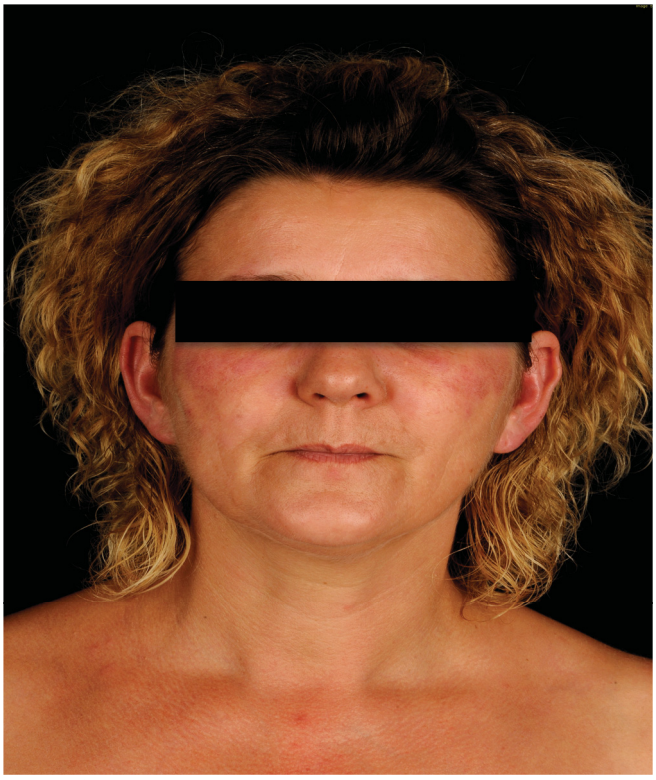

Figure 9: Lupus like dermatitis during therapy with etanercept

4.3 Granulomatous diseases: granuloma annulare and interstitial granulomatous dermatitis

Granuloma annulare (GA) is considered a benign skin disease presenting with erythematous papules and/or annular plaques most commonly localized to the distal extremities and typically affecting women.[74, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271]

It may also manifest as generalized GA, characterized by small asymptomatic papules that may cover the whole body.[272] The disease can be associated with underlying conditions, such as diabetes mellitus and thyroid diseases.[273] Histologically, GA is characterized by anecrobiotic center surrounded by a cellular infiltrate composed of T-cells and macrophages. Treatment of GA comprises topical and systemic corticosteroids, cyclosporin, retinoids and PUVA therapy. More recently, TNF-α inhibitors have been used successfully.[274, 275, 276]

However, paradoxically TNF-α inhibitors have also been shown to induce GA. Six patients received adalimumab, three infliximab and one patient etanercept, respectively. Nine patients were suffering from RA and one patient from PsA [89, 230] In three patients anti-TNF-α treatment was stopped and GA subsequently showed remission. In seven patients, treatment with the TNF-α antagonists was continued, while applying topical steroids with a good clinical result. Interstitial granulomatous dermatitis (IGD) is often associated with immune-mediated diseases like RA, LE and vasculitis.[74] Clinically it manifests linear papules or plaques on extremities or the lateral sides of the trunk.[74]

Kreuter el al successfully used infliximab for the treatment of IGD.[277]

IGD was observed in patients with RA and PsA undergoing treatment with infliximab, etanercept and adalimumab.[72, 269, 278]

Discontinuation of TNF-α inhibitors led to remission in three patients. However, continuation of anti-TNF-α therapy did achieve conflicting results, resulting in resolution of IGD in one case (using additionally topical steroids) and persistence in the others.[269, 278]

4.4 Stevens-Johnson syndrome

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but potentially life-threatening diseases. [279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292] Besides systemic corticosteroids and intravenous immunoglobulins, TNF-α inhibitors have been successfully administered in SJS and TEN patients.[292, 293, 294] However, TNF-α inhibitor induced SJS and TEN have also been reported. According to a FDA Drug Safety Letter, 11 cases of SJS and 5 cases of TEN as well as two combined cases have been observed [113, 207] Adalimumab, etanercept and infliximab have been reported as causative agents[86, 114, 207, 295, 296] Most patients were female and suffering from RA. In any case TNF-α inhibitors have to be discontinued in patients with SJS and TEN.[207]

4.5 Alopecia areata

Alopecia areata (AA) is an autoimmune disease, which causes hairloss on any hair-bearing area.[297] The disease is non-scarring and can develop in various clinical manifestations.[297] Patients can either lose their hair all over the body (alopecia universalis), or may suffer from patchy hair loss, which is sometimes reversible.[297] Alopecia areata can be associated to other autoimmune diseases such as thyroid diseases, vitiligo and systemic lupus erythematosus (SLE).[297] According to a review article by Gilhar al[297], no sex predilection has been found. However**,** in a Chinese study, men have been reported to be more often affected than women (male to female ratio: 1.4: 1).[298, 299]

The pathogenesis of alopecia is still not fully understood. It is thought that AA $CD4^+$ and $CD8^+$ play a major role in the pathogenesis of AA.[300, 301] Cytokines that have been shown to be potent inhibitors of hair growth comprise IL-1α, IL-1β and TNF-α.[302, 303, 304] Therefore Strober and al investigated the role of etanercept in patients suffering from AA in an open label study. Interestingly they could not prove that the inhibition of TNF-α led to a significant improvement of severe AA.[70] In 2004 Ettefagh et al[305] reported for the first time that AA was induced by infliximab in a patient with rheumatoid arthritis and Sjögren's syndrome. Since this first report 48 patients (aged 7-69 years; 25 women and 18 men; [The gender was not given for 5 patients]) have been reported to suffer from TNF-alpha induced alopecia.[83, 167, 279, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323,

[324, 325, 326, 301] In five patients the gender and age were not given in the respective paper.[311, 315] Fourteen patients were suffering from Crohn's disease, thirteen from rheumatoid arthritis (RA), twelve from psoriasis/psoriatic arthritis, seven from ankylosing spondylitis and one each from Behcet's disease and juvenile idiopathic arthritis (JIA), respectively.[311, 315]

The onset of this disease after initiating TNF-α treatment ranged between a few days[300] and three and a half years.[286] 24 patients received adalimumab, 17 infliximab and six patients etanercept, for one patient suffering from ankylosing spondylitis the TNF-α inhibitor used was not given.[315] In most cases, alopecia occurred rapidly, involving parietal and occipital sides.[167, 279, 280, 281, 282, 283, 284, 286, 287, 288, 301] The clinical spectrum of alopecia displayed a broad variety ranging from diffuse alopecia to alopecia universalis and comprised scarring alopecia in one patient.[292, 298] No previous history of alopecia was noted in the majority of patients. Interestingly some patients developed also additional halo nevi[283] and psoriasiform eruptions.[167, 292, 298, 300, 296, 291] TNF-alfa treatment was discontinued in 25 patients and continued in ten patients. Two patients were switched to adalimumab and certolizumab pegol, respectively.[296, 300] In six patients no details were given concerning further TNF-α therapy. Furthermore topical treatment was initiated almost all patients.

Histopathology revealed the following follicular changes: an increase in catagen/telogen and miniaturized hairs, as well as peribulbar inflammation[322] Furthermore, increased numbers of eosinophils and plasma cells were detectable in patients with TNF-α induced alopecia, whereas the aforementioned cells are rarely seen in psoriatic alopecia or classic AA.[322] However, differentiating between anti-TNF-α induced alopecia and classic AA as well as psoriatic alopecia can be a clinical challenge. Doyle et al proposed the following features suggesting the diagnosis of anti-TNF-α induced alopecia: development of psoriasis/psoriasiform eruption after initiating anti-TNF-α treatment, no previous history or presence of psoriasis and the development of psoriasiform lesions on other parts of the body than the scalp.[322] The pathogenesis of anti-TNF-α induced alopecia is not yet known and remains still elusive.

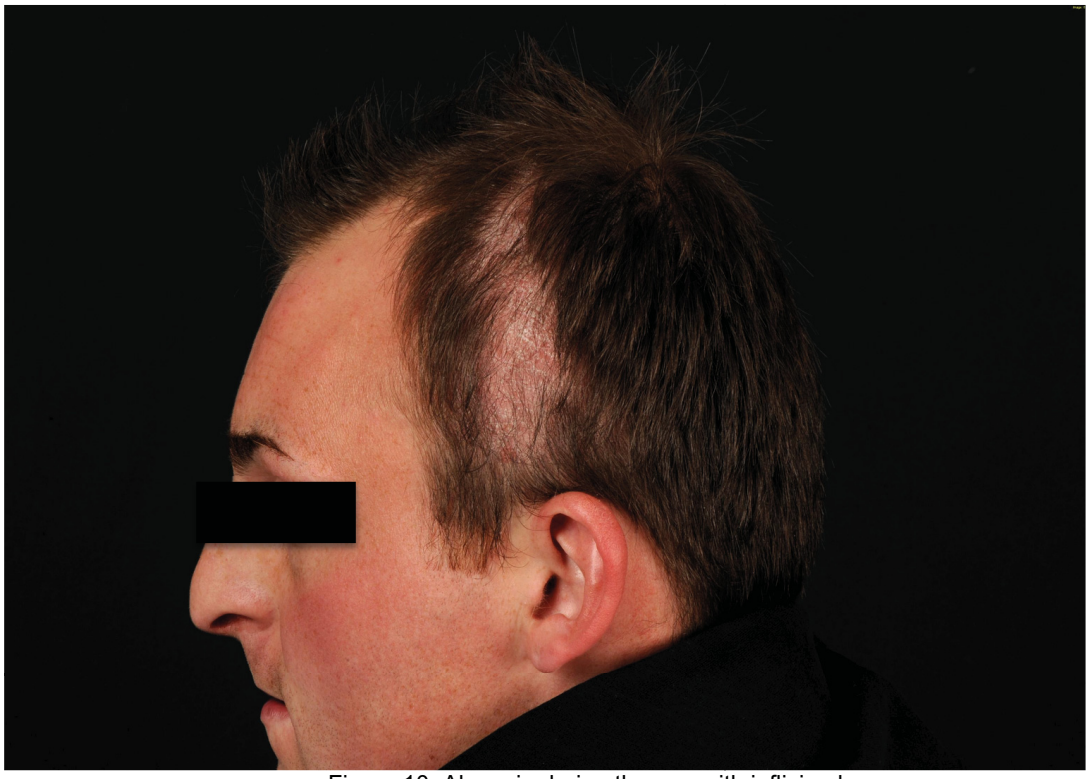

Figure 10: Alopecia during therapy with infliximab

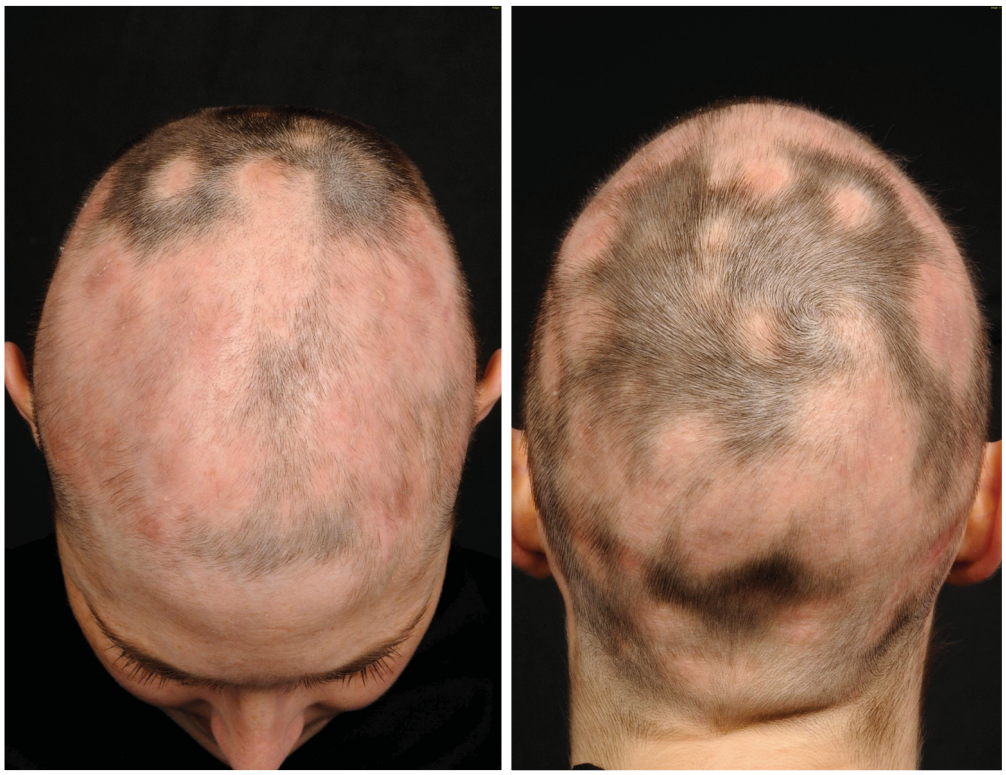

Figure 11: Infliximab induced alopecia

4.6 Cutaneous Infections

Cutaneous infections are one of the most common side effects of TNF-α inhibitor therapy.[73, 207, 327, 328, 329, 330, 331, 332, 333]

The skin has been found to be the second most common site of serious infections after the respiratory tract.[90, 333] Pathogens most commonly implicated in cutaneous infections, have been shown to be either bacterial, viral, fungal or parasitic.[73, 207, 334] Some infections are uncommon in the Western hemisphere (e.g. Europe and/or the USA) and therefore the true incidence might not be adequately addressed.[334] Underreporting of infectious cutaneous adverse effects might also be a further reason for not capturing the true incidence of cutaneous infections. Using data from the British Society for Rheumatology Biologics Register (BSRBR), the risk for serious cutaneous infections has been found to be highest in the first six months of anti-TNF-α treatment.[335] However, one has to admit that some patient populations, especially RA patients are more prone to suffer from infections independently from treatment than for example patients with psoriasis.[334, 336, 337] Dommasch 2011]. The incidence for bacterial infections (e.g. abscess formations, cellulitis and erysipelas) in patients under anti-TNF-α therapy ranges from less than 0.1 % to 7%.[81, 91, 117] Herpes infections (e.g. herpes zoster, herpes simplex and primary varicella) have been noted to range from 0.8% to less than 5% in TNF-α inhibitor treated patients.[83, 91, 207, 338, 339, 340] Incidence rates for fungal infections ranged from 1% to up to 6.9%.[81, 83, 91] Cutaneous infections should be treated appropriately and anti-TNF-α therapy should be paused until the infection is cured.[73, 207, 350]

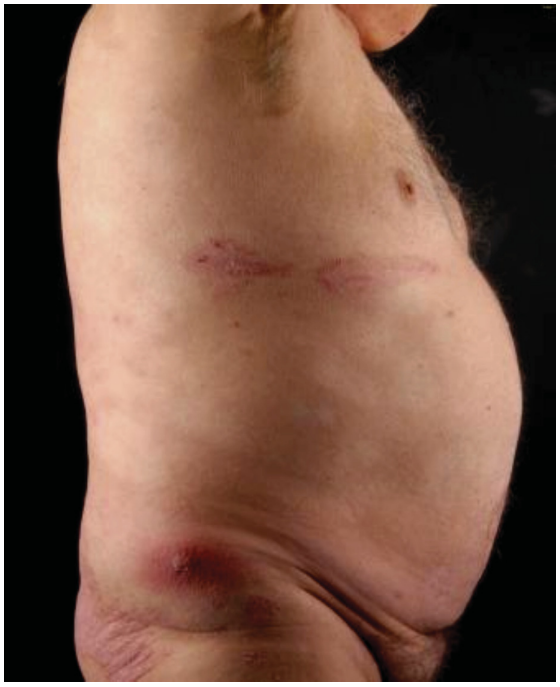

Figure 12: Abscess in a patient under treatment with etanercept

4.7 Cutaneous Vasculitis

TNF-α inhibitors, especially infliximab have been used successfully in treating steroid refractory vasculitis. [341, 342, 343, 344, 345, 346, 347, 348],whereas etanercept was found to be ineffective as a treatment option of Wegener's granulomatosis.[96] However, vasculitis was also observed as a further paradoxical side effect of anti-TNF-α therapy. Ramos-Casals et al.[76] reviewed 113 patients developing vasculitis under TNF-α inhibitor therapy. The underlying disease was RA in the majority of patients and most patients were female.[76, 349] Besides RA, patients with AS, CD, JRA and PsA were also affected.[76] The clinical spectrum showed a great variety ranging from purpura, ulcerative and blistering lesions, focal and diffuse nodules, chilblains, digital vasculitis, erythrocyanosis, livedo and maculopapular rashes.[76, 349] Noteworthy, visceral involvement concerning the peripheral nervous system and the kidneys was observed in 245 of cases.[76, 349]

TNF-α inhibitors inducing vasculitis comprised etanercept and infliximab, and to a much lesser degree adalimumab.[76] In most cases (89%) anti-TNF-α therapy was discontinued after manifestation of vasculitis, and complete resolution was achieved in 67% and partial resolution in 25% of patients.[76] Besides stopping anti-TNF-α therapy, systemic corticosteroids and immunosuppressive agents were used. By rechallenging patients with the same or a different TNF-α inhibitor 12 out

of 16 patients did experience another vasculitis bout.[76] However, it is noteworthy that patients with severe seropositive RA may also develop vasculitis per se without anti-TNF-α therapy.[74] Otherwise a causal relationship between anti-TNF-α therapy and vasculitis seems to be given, as also patients with different diseases like PsA and CD were reported to develop TNF-α inhibitor induced vasculitis.

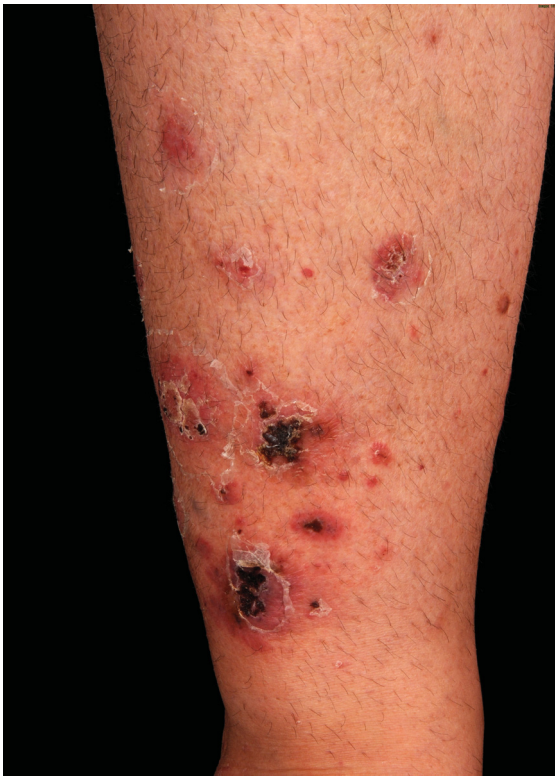

Figure 13: Vasculitis during therapy with adalimumab

4.8 Infusion Reactions

According to a study by Moustou et al, infusion reactions after the intravenous administration of infliximab are not an infrequent event.[350]

There are two different types of infusion reactions. Reactions, which occur during an infusion or within 24 hours after the infusion, are defined as acute reactions. [351, 352] Reactions, which occur 24 hours to 14 days after an infusion, are defined as delayed-type hypersensitivity reactions.[365] Acute reactions may manifest as urticaria, erythematous rash, fever, chills, dyspnoea, bronchospasm, laryngeal oedema and hyptotension.[365] Recent Studies revealed that 20% out of 5707 patients treated with Infliximab suffered from an acute reaction.[361, 353] Recent

studies revealed that infliximab leads in 3% to 22% of all patients to mild, moderate or severe infusion reactions.[103, 354, 355]

"*Mild reactions are defined self-limiting and resolve spontaneously after temporary cessation of the infusion or reduction of the infusion speed. Moderate reactions are those that require closer attention and an extended observation period and often discontinuation of the Infusion. Serious reactions involve respiratory symptoms or a symptomatic blood pressure drop and need for close monitoring, often for 24 h and occasionally requiring hospital admission*."[356, 358]

Cutaneous reactions due to the infusion of TNF-alfa blockers may appear as a burning sensation with erythema, flushing and urticarial rash. There have been reports of a "red- man syndrome" like reaction caused by infliximab, which resembles a rapid injection of vancomycin.[357]

Less than 1% of these reactions results in discontinuation of the treatment and require immediate treatment. Usually the downgrade of the infusion rate leads to an improvement of most symptoms. These reactions are mostly recognised as a non-immunomediated type and are not recognized as a true anaphylactic response. Specific prophylactic measures like premedication with antihistamines or corticosteroids should be taken, if the appearance of mild or moderate infusion reactions can be expected. However, according to Lecluse et al there is no proof of the effectiveness of prophylactic medication.[358]

During the last few years, acute reactions caused by infliximab have decreased. This is most probably due to the experience doctors gained concerning the treatment with anti- TNF-alfa agents.[359]

Delayed-type hypersensitivity reactions may appear in about 1% to 2.5% of all patients, which are treated with infliximab. These reactions usually manifest as fatigue, myalgiasis, arthralgiasis, sore throat, dysphagia, headache, fever, facial oedema and urticarial eruption.[358] Unlike acute reactions, delayed type reactions are supposed to be immune mediated type 3 hypersensitivities.[103, 354]

A decline in clinical responses have been discovered, which are probably caused by the neutralizing actions of antibodies established against infliximab.[354]

In order to create an immune tolerance against infliximab, various treatments have been proposed, such as the administration of immunosuppressive drugs and constant infusions in order to prevent long intervals during the treatment.[358]

Anti-etanercept antibodies have been discovered in patients medicated with etanercept, however they do not seem to be connected either with adverse reactions or with clinical responses.[360]

	Occurence	Management	Reaction
Acute Reaction	During infusion- 24 h after an infusion	Slowing infusion rate, intravenous fluids, paracetamol, antihistamines	urticaria, erythematous rash, fever, chills, dyspnoea, bronchospasm, laryngeal oedema and hyptotension
Delayed Reaction	24h- 14 days after an infusion	Paracetamol, antihistamines, steroids	fatigue, myalgiasis, arthralgiasis, sore throat,dysphagia, headache, fever, facial oedema and urticarial eruption

Table 3: Summary of accute and delayed infusion reactions (modified according to Lecluse et al)

4.9 Injection Site Reactions

According to to recent studies, etanercept, adalimumab and certolizumab pegol can cause injection site reaction, which consist of mild to moderate erythema, itching, tenderness and swelling at the site of the injection.[207, 261, 350] 20% to 37% of all patients treated with TNF-α blockers are affected by injection site reactions within the first months of their medical care.[207, 350] Usually, these incetion site reactions are mild and last for three to five days.[361] However the longer the treatment lasts, the fewer these reactions may occur.[362 363 364] Etanercept is supposed to cause injection site reactions more likely than adalimumab or certolizumab pegol. This is due to the fact that etanercept is used for a longer time than adalimumab and certolizumab. Additionally, more patients had been treated with etanercept and in higher dosage[365]

Few patients treated with etanercept experience so-called recall reactions when receiving another injection[366]. Histologic and immunophenotypic studies uncovered that CD4+ lymphocytes can appear in injection site reactions and CD81 lymphocytes may occur in recall reactions.[362]

Studies concerning adalimumab revealed that 6% to 12% of all patients treated

with this anti TNF-α medication can be affected by injection site reactions, which also manifest in erythema, itching, tenderness and swelling.[367] [105] Patients suffering from an injection site reaction can be treated with ice, topical steroids and pain control. Furthermore, changing injection sites may help to avoid injection site reactions. In general, if an injection site reaction occurs, TNF-α treatment will not have to be terminated.[365]

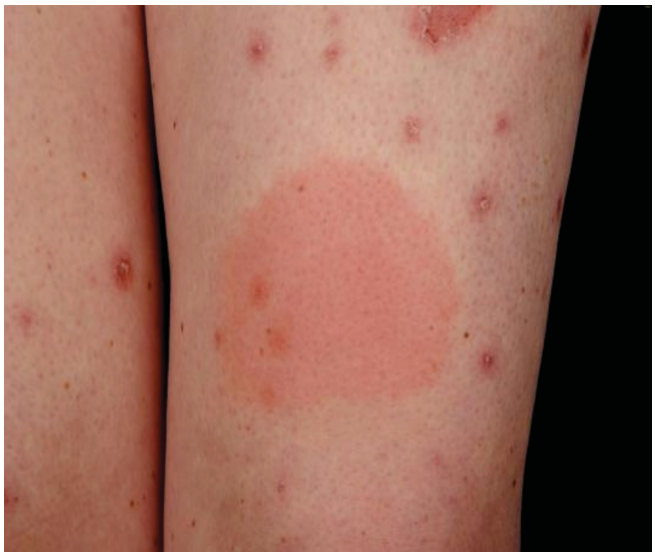

Figure 14: Etanercept induced injection site reaction

4.10 TNF-α inhibitors and skin cancer

There has been quite a controversial debate as to whether TNF-α inhibitors lead to an increase in cancer rates.[73, 350, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386]

First, TNF-α by itself is a highly pleiotropic cytokine.[13] In animal models, it has been shown to induce tumor regression as well as tumor progression.[386] Second, one has to consider the possible potentiating effect of immunosuppressive and anti-psoriatic therapies (e.g. sun exposure, PUVA treatment and administration of drugs like methotrexate and cyclosporin A).[386, 387]

It is also noteworthy that an increased risk for malignancies has been observed in patients with RA and psoriasis even without a history of anti-TNF-α treatment.[51, 386, 388, 389, 390]

Mercer et al studying data from the BSRBR were able to show that the overall risk for skin cancer in RA patients (regardless of their treatment history) is increased

compared to the general population.[391] Lebwohl et al found no increased risk for NMSC in patients treated with etanercept. In 1,442 patients with RA only four patients with 4 squamous cell cancers were detected. Postmarketing data published in this study indicated 1 incident per 10,000 patient years.[384] Furthermore, no increase regarding the skin cancer risk was found by Mercer et al.[391] analyzing data from BSRBR. This finding has been in line with a metaanalysis done by Lembruno et al.[392] No increased short term risk concerning overall malignancy and NMSC in patients treated with certolizumab and golimumab was also noted in a metaanalysis performed by Le Blay et al.[393] In contrast to these results, Askling et al found in their metaanalysis published in 2011 a twofold increased skin cancer risk.[394] Chakravarty et al also observed in a cohort study in 15,789 RA patients and 3639 osteoarthritis patients an increased risk for NMSC (hazard ratio for anti-TNF-α alone 1.24 and 1.97 in patients with anti-TNF-α and MTX) as did a meta-analysis including 3493 RA patients receiving adalimumab or infliximab[235], which found an increased risk for malignancies (OR 3.3) in patients under anti-TNF-α therapy. However, one should note that over the last years the induction or rapid activation of latent skin cancers in some patients treated with TNF-α inhibitors has been observed.[102, 395, 396] Furthermore, malignant melanoma has only been rarely reported in patients with anti-TNF-α therapy.[106, 377, 397, 398, 399] Kowalzick 2009, Khan 2009As data are conflicting, larger studies are clearly needed to further clarify this important issue. Till then a thorough screening for skin cancer in patients that are considered to receive anti-TNF-α therapy and an annual skin examination for skin cancer are strongly warranted.

5 Discussion

The introduction of TNF-α inhibitors has significantly changed the treatment in patients suffering from immune-mediated diseases like psoriasis, PsA, RA, AS and the IBDs. So far these drugs have been shown to be efficient and relatively safe. However, with the increasing use of these agents side effects were noted more commonly. Cutaneous adverse events have been observed with all approved TNF-α antagonist (adalimumab, certolizumab, etanercept, golimumab and infliximab) in recent years. A great variety of different skin diseases have been reported in association with the use of TNF-α inhibitors ranging from psoriasis, lichen planus, alopecia, lupus like eruptions, vasculitis, injections side reactions as well as infusion reactions, to eczema and various different skin cancers.[73, 74, 350, 365]
In a recent article by Moustou et al the authors tried to estimate the strength of association with the corresponding skin diseases.[350] They found definite associations with injection side reactions, as well as with infusion reactions (acute as well as delayed ones), strong associations were observed with psoriasis and psoriasiform eruptions, lupus like disease, vasculitis and bacterial, viral and mycotic infections.[350] Eczema, non tuberculosis mycobacterial infections and granulomatous reactions were considered to be moderate to strong associations [Moustou]. Interestingly, the strength of association with malignancies (NMSC, cutaneous lymphomas, and melanoma) was found to be poor.[350, 400]
Importantly, one must note that TNF-α inhibitors are capable to induce highly paradoxical skin reactions. TNF-α inhibitors are nowadays a mainstay in the treatment of moderate to severe psoriasis and PsA[8], however they may also induce psoriasis and/or psoriasiform eruptions in patients treated with anti-TNF-α medication for other reasons than psoriasis. It is noteworthy that the majority of patients with TNF-α inhibitor induced psoriasis suffer from different diseases like RA, CE, UC, and AS. However, a few patients were initially suffering from psoriasis and experienced worsening of their disease or a change of their psoriasis phenotype under anti-TNF-α treatment. Switching to a different TNF-α inhibitor or rechallenge led to a reappearance of psoriasis in some of the affected patients.

This phenomenon has also been reported for other cutaneous side effects, for example in patients with TNF-α-induced lichen. Therefore, a class effect was suspected. Whether patients had to discontinue anti-TNF-α treatment or were able to go on depends also on a variety of different factors. The severity of the cutaneous side effect as well as the severity of the underlying disease and the possible treatment options for these diseases have to be taken into consideration. In a number of patients topical therapy without discontinuing anti-TNF-α therapy led to an improvement of the cutaneous adverse effect. Until now no markers or clinical indicators are available to predict in which patient continuation of anti-TNF-α therapy is safe and useful. Importantly, the exact pathomechanism of these paradoxical cutaneous side effects still remains unclear. Patients of all ages and of both sexes were reported to be affected.

The real prevalence and incidence of these cutaneous side effects are not yet known. Underreporting of cutaneous side effects must be considered to be a major reason for this as well as the great variability in reporting the published data. Whether there is a preference for one sex is still under debate as numbers of affected patients are small, and the exact prevalence and incidence rates are not yet known. To clarify these questions more data are clearly warranted.

Registries like the BSRBR are a first step in this direction. However, these registries should comprise all patients treated with TNF-α inhibitors. As only a subset of patients develops these cutaneous side effects, genetics have also been implicated to play a pivotal role. Therefore, research efforts in the field of pharmacogenetics might also prove to be a valuable tool in providing a better insight in the pathogenesis of these side effects.

Furthermore, accurate diagnosis of cutaneous side effects, preferrable by dermatologists, is of utmost importance. Last but not least, reporting of cutaneous side effects should be done by all physicians treating patients with TNF-α antagonists in order to to improve our knowledge of these adverse events and also to detect rare but potentially life-threatening side effects.

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Infliximab: www.fda.gov./cder/foi/label/2007/103772s589lbl.pdf;

adalimumab: www.fda.gov./cder/foi/label/2008/125057s114lbl.pdf;

etanercept: www.fda.gov./cder/foi/label/2008/103795s5359lbl.pdf;

certolizumab pegol: www.cimzia.com/pdf/CIMZIA%20PI%20032008.pdf

(all websites accessed 1 November 2008)

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