Abstract
Inflammatory skin diseases represent an important part of dermatological pathology. Recent advances in the understanding of inflammatory processes have identified various cytokines, and in particular Tumor necrosis factor (TNF) as a potent and central proinflammatory cytokine involved in many conditions, including rheumatic, gastrointestinal tract, and skin diseases. Therefore, inhibition of TNF has become a major therapeutic target in the treatment of inflammatory disorders. Thalidomide is one of the first TNF inhibitors that have been used. It was initially prescribed by chance and pragmatically by dermatologists in inflammatory diseases such as erythema nodosum leprosum, lupus and severe aphthosis, but its identification as an inhibitor of TNF is more recent. The discovery of the major role of TNF alpha in the physiopathology of certain inflammatory diseases and notably in rheumatoid arthritis and Crohn's disease has led to the emergence of 3 new anti-TNF alpha drugs. These so-called biologics are two monoclonal antibodies (infliximab and adalimumab) and one fusion protein composed of a soluble TNF alpha receptor [...]

Reference

DOI : 10.13097/archive-ouverte/unige:6447

Available at: http://archive-ouverte.unige.ch/unige:6447
TNF inhibitors in Dermatology
From Thalidomide to Biologics

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Février 2010
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Quand le disciple est prêt, le Maître apparaît...

Je tiens à remercier mon Maître le Professeur Jean-Hilaire Saurat pour son accueil, son soutien et son enseignement tout au long de ces dernières années (bientôt 10 ans...). Je peux vraiment dire qu’il m’a ouvert les yeux, et montré la Dermatologie comme jamais personne ne l’avait fait jusqu’à ce que j’ai la chance inestimable (il y a bientôt 10 ans, donc) de le rencontrer...Lorsque je vins à Genève à la fin de mon internat, en Janvier 2000, ne sachant pas trop (pas du tout) à quel endroit serait mon avenir, le proverbe Zen cité ci-dessus prit alors tout son sens...

Mes remerciements également aux Doctoresses Anne Marie Thielen et Caroline Barde et au Docteur Gionatta Marazza pour leur travail sur les biothérapies à Genève, au Professeur Jean Revuz pour m’avoir mis le pied à l’étrier de ce cheval de bataille qu’est pour moi le thalidomide depuis plusieurs années, au Docteur Jean Dudler pour son aide et son amitié, et au Professeur Renato Panizzon pour m’avoir laissé la liberté de développer l’usage des biothérapies à Lausanne avant de revenir à Genève...

Je dédie ce travail à mes grands parents (je pense souvent à vous cinq même si je n’en ai connu que quatre...) et en particulier à mon grand père le Docteur Maurice Leconte qui fut un pionnier dans son domaine, à mon père le Docteur Jacques Laffitte malheureusement parti trop vite, à ma mère Agnès toujours présente quand il le faut.

Et merci à ma petite famille, Laurence mon épouse, Jules et Lucas, qui m’entourent de leur joie de vivre et de leur amour joyeux et désordonné...

Genève, le 4 février 2010
Introduction

TNF inhibition: old and new dreams

Inflammatory skin diseases represent an important part of dermatological pathology. Recent advances in the understanding of inflammatory processes have identified various cytokines, and in particular Tumor necrosis factor (TNF) as a potent and central proinflammatory cytokine involved in many conditions, including rheumatic, gastrointestinal tract, and skin diseases. Therefore, inhibition of TNF has become a major therapeutic target in the treatment of inflammatory disorders. Thalidomide is one of the first TNF inhibitors that have been used. It was initially prescribed by chance and pragmatically by dermatologists in inflammatory diseases such as erythema nodosum leprosum, lupus and severe aphtosis, but its identification as an inhibitor of TNF is more recent. The discovery of the major role of TNF alpha in the physiopathology of certain inflammatory diseases and notably in rheumatoid arthritis and Crohn's disease has led to the emergence of 3 new anti-TNF alpha drugs. These so-called biologics are two monoclonal antibodies (infliximab and adalimumab) and one fusion protein composed of a soluble TNF alpha receptor (etanercept) specifically directed against TNF. The first clinical data are very impressive, but new and unexpected side effects have progressively been described. These powerful drugs are increasingly prescribed, and the aim of this work is to summarize the recent knowledge on the old (thalidomide) and new (biologics) TNF inhibitors in dermatological diseases.
Part I

TNF in Dermatological diseases

1- Biology of TNF

Tumour necrosis factor (TNF) is a proinflammatory cytokine that plays a key role in most of the inflammatory processes, as well as in immune responses to infections and tumour antigens [1]. Human TNF-alpha, which is located on chromosome 6, is translated as a 233 amino acid, 26-kDa proprotein that lacks a classic signal peptide. Newly synthesized proTNF-alpha is first displayed on the plasma membrane and is then cleaved in the extracellular domain to release the mature monomer through the actions of matrix metalloproteases, the TNF-alpha converting enzyme (TACE) toward a soluble 17-kDa protein made up of three subunits [2]. This molecule stands at the beginning of a proinflammatory cytokines cascade and triggers off proinflammatory signals at the target cell by binding to membrane TNF receptors. Two different receptor types are known: a 55-kDa (TNF-RI) and a 75-k Da receptor (TNF-RII). Both TNF-RI and TNF-RII exist as cell-surface and soluble forms, and both forms bind TNF, although with different affinities [3]. TNF cell-surface receptors are present on nearly all cell types, including macrophages, lymphocytes, and neutrophils [2]. TNF must bind to two or three cell-surface receptor molecules for signal transduction to occur. Numerous biological effects of TNF are mediated by the intracellular signalling of the high-affinity TNF-RI receptor [4] as well as the low-affinity TNF-RII receptor [5]. Soluble receptors antagonize this proinflammatory cytokine by binding free TNF [3].

TNF may play a role in normal tissue homeostasis as low levels of TNF are produced by macrophages under physiologic conditions [6]. In disease, TNF is produced in increase amounts by macrophages, T cells, mast cells, neutrophils, dendritic cells, fibroblasts, keratinocytes and endothelial cells in response to infection, tissue injury or inflammation [7]. TNF is a pro inflammatory cytokine with pleiotropic effects which increases the recruitment of leukocytes to the site of inflammation through increased adhesion molecules expression, increase vascular permeability, secretion of metalloproteinases and stimulation of other cytokines and chemokines (IL-1, IL-6, IL-8, GM-CSF) [2]. Much recent work has demonstrated that soluble TNF (solTNF, signalling primarily through TNFR1) and transmembrane TNF (tmTNF, signalling through both TNFR1 and TNFR2) have distinctly different, and potentially opposing, functions in inflammation.
and immunity. Several knockout and knockin mice have been widely used to show that tmTNF is
crucial in maintaining a normal innate immune response to infections including listeria, leishmania
and tuberculosis [8].
Taken together, results from genetic models suggest that soluble TNF (probably signalling through
TNFR1) may be necessary and sufficient to drive inflammation, while by contrast tmTNF (possibly
signalling through TNFR2) may be essential to maintain immunity to infections, and to tolerize
autoantigens [8, 9].

2- TNF in cutaneous inflammatory disorders
This TNF mediated induction of proinflammatory cytokines, leukocyte chemotaxis and
angiogenesis play a fundamental role in autoimmune diseases like rheumatoid arthritis (RA),
Crohn’s disease, Psoriasis or other inflammatory diseases of the skin, diseases that are characterized
by elevated TNF-serum concentrations, sometimes fever and an increase of acute-phase proteins.
The approach of treating inflammatory diseases by blocking TNF has been confirmed by the
dramatic success of thalidomide in aphtosis and erythema nodosum leprosum, and the TNF blockers
infliximab, etanercept and adalimumab in RA, juvenile idiopathic arthritis, Crohn’s disease,
psoriasis or additional chronic inflammatory dermatoses [10-13].
2.1 Psoriasis
Overexpression of TNF has been well demonstrated in psoriasis [2]. In lesional psoriasis skin, and
to a lesser extent in uninvolved psoriasis skin, TNF was found to be distributed throughout the
epidermis and was also specifically localized to the upper dermal blood vessels [14]. Other authors
have localized TNF in psoriatic lesions with dermal macrophages in the papillary dermis and
focally by keratinocytes and intraepidermal Langerhans’ cells but did not find it to be significantly
expressed in endothelial cells, mast cells, or dermal Langerhans’ cells [15]. Importantly, the two
receptors for TNF are differentially expressed in the skin. In normal skin, and uninvolved and
lesional skin from psoriasis patients, the p55 TNF-RI is associated with epidermal keratinocytes and
a network of upper dermal dendritic cells. In contrast, staining of the p75 TNF-RII in normal skin
was found to be restricted to eccrine sweat ducts and dermal dendritic cells, and was absent from
the epidermis [14]. Furthermore, a significantly elevated TNF plasma concentration was found in
psoriatic patients [16]. High levels of TNF have also been detected in psoriatic arthritis. The pattern
and the expression levels of proinflammatory Th1 cytokines, TNF and IL-1b were found to be
similar in synovial tissue of psoriatic arthritis when compared to rheumatoid arthritis [17].
2.2 Other cutaneous inflammatory disorders:
TNF plays a major role in infectious and non infectious granuloma formation [18]. Its implication
has been studied in various systemic granulomatous diseases such as tuberculosis, sarcoidosis and
oral Crohn’s disease lesion [19]. In sarcoidosis, high levels of TNF are correlated with disease
activity and progression [18], and the same correlation have been established in erythema nodosum leprosum [20] or in Behçet’s disease [21].

In some other cutaneous diseases, the role of TNF was less expected:

- In pemphigus vulgaris, which is used as a prototype for an autoimmune dermatosis with blister formation, there is no clear evidence of a central role for TNF (and IL-1) in the pathogenesis of blister formation [12]: in vivo an increased expression of TNF and IL-6 is found at the direct site of intraepidermal adhesion loss [22]. If, however, in vitro cultures of human keratinocytes receive anti-TNF antibodies before coculturing with IgG antibodies from pemphigus patients, the phenomenon of intercellular adhesion loss is absent [22]. This protective effect of blocking TNF can be reproduced in vivo [12].

- Atopic dermatitis is a model of Th2 cytokine mediated cutaneous disease [23]. However, in the pathogenesis of atopic dermatitis, TNF is released initially by infiltrating mast cells and later by invading T-helper lymphocytes, as well as epidermal keratinocytes. TNF is involved in the up-regulation of proinflammatory cytokines, such as IL-1, 6 and 8 and of adhesion molecules, such as ICAM-1 and VCAM, on keratinocytes and vascular endothelial cells, thereby facilitating the migration and adhesion of inflammatory cells in the epidermis [23].

- Furthermore, in Netherton syndrome (NS), which is a genodermatosis with features of atopic dermatitis, inflammatory cutaneous flares and ichthyosis caused by mutations in SPINK5 (a gene encoding the protease inhibitor lymphoepithelial Kazal-type–related inhibitor (LEKTI)), it has been recently shown that pro-inflammatory cytokines such as TNF, are overexpressed [24] as well as the pro-Th2 cytokine thymic stromal lymphopoietin (TSLP).
Part II

Thalidomide: an old drug with new clinical applications


1- Introduction

Thalidomide was first synthesized in 1954 by the German pharmaceutical firm Chemie Grünenthal, and marketed in Europe in October 1957 as an antiemetic and nonbarbiturate sedative hypnotic [25]. The first pharmacological studies performed on rodents showed a fast sedative effect and remarkably low toxicity even at high doses. Between 1957 and 1961 thalidomide became widely used by pregnant women for its anti-emetic effect from morning sickness [26]. A significant teratogenic effect of thalidomide was reported in 1961 [27] after the rise in reported cases of phocomelia, a previously exceptional congenital malformation. Nearly 6000 cases of internal or external deformities were attributed to thalidomide during this period [26, 28] and the drug was withdrawn from the market. In 1965, a dramatic improvement of erythema nodosum leprosum (ENL) treated with thalidomide was reported by Sheskin [29], and the discovery in 1991 of thalidomide’s anti-Tumor Necrosis Factor (TNF)-α activity [30] led to renewed interest in this drug. Since then, this anti-TNF-α effect has been studied, with several clinical indications under investigation. There are two main strands to current research: immunomodulatory action in various inflammatory diseases, and antiangiogenic action which seems to be of interest in oncology.

2- Pharmacology

Thalidomide, or α-N-pthalimido-glutarimide, is a glutamic acid derivative (figure 1). The molecule is a racemic mixture of the S (-) and R (+) isomers. There is some evidence to suggest that the two enantiomers act differently: the R form could be responsible for the sedative effect [31], while the S form could have the immunomodulatory, antiangiogenic [32] and teratogenic properties, although this hypothesis is debatable [33]. However, in human, this difference is not relevant since chiral interconversion between the two enantiomers leads in vivo to a racemic mixture in two hours [34].
Fig 1: Chemical structure of Thalidomide and Lenalidomide. Lenalidomide is a second generation analogue of thalidomide that shares a similar chemical structure; this drug is found to be 50 000-fold more potent in inhibiting TNF in vitro compared to the parent compound (cf infra).

The solubility of this lipophilic molecule is low in water and alcohol, and the molecule is sensitive to hydrolysis for pH higher than 6 [25, 35].

The pharmacokinetics of thalidomide has been studied both in humans and animals [36-39]. After oral absorption, the plasmatic peak in healthy volunteers is reached in 3.2 +/- 1.4 to 4.39 +/- 1.27 hours (Tmax) [36, 37]; and is delayed by a high-fat meal [40]. The apparent distribution volume is very broad: 120 liters [38] with a fast penetration of the hemato-encephalic and placental barriers.
Studies in animal showed that thalidomide was distributed in all the tissues with a predilection for digestive tract and kidneys [42]. The main metabolic pathway is probably non-enzymatic hydrolysis, leading to at least 12 breakdown products; some of them could have their own pharmacological activity [43]. Hydroxylated products have also been detected, suggesting that enzymes from the hepatic P-450 cytochrome family could be involved [44].

Excretion of thalidomide and its metabolites is mainly through the renal route. The plasma half-life ranges from 6.17 +/- 2.56 to 8.70 +/- 4.11 hours [36-38]. Excretion of thalidomide in semen was studied in rabbits. After two oral doses separated by 18 hours, thalidomide was found in semen from the sixth hour until the twelfth day. Thalidomide was not only present in the seminal fluid, but also firmly fixed on spermatozoans [45]. In humans, thalidomide is also present in semen. After an oral intake of 100 mg/day, thalidomide was detected in semen at week 4 with a correlation between plasma and semen levels [46].

In a recent study, the pharmacokinetics of a single oral dose of 100 mg or 200 mg of thalidomide was assessed in 14 asymptomatic HIV-infected men [47]. The results were overall consistent with those given previously, with respectively for 100 and 200 Mg: Tmax of 2,5 +/- 1,5 H and 3,3 +/- 1,4 H, a half-life of 4,6 +/- 1,2 H and 5,3 +/- 2,2 H, an apparent distribution volume of 70 +/- 16 L and 83 +/- 35 L.

There is no parenteral preparation for thalidomide. The dermal absorption of thalidomide is very low and this molecule may not be appropriate for topical delivery. Analogues have been synthesized, and a methyl derivative could have a better dermal penetration [48]. Thalidomide enhances the activity of alcohol, barbiturates, chlorpromazine and reserpine [35, 44], but does not affect the pharmacokinetics of orally administered hormonal contraceptives [49].

### 3- Biological properties

**3.1 Hypnosedative action**

The sedative properties of thalidomide are not well understood. Thalidomide acts by a different mechanism than barbiturates, possibly involving activation of sleep centers that depend on gamma-aminobutyric acid (GABA) receptors [38]. The effect on sleep is very particular, different from all other hypnotic drugs by increasing the time spent in phase 3-4 and REM (rapid eye movement) and decreasing the time spent in phase 1 [50]. This sedative action is preferentially related to enantiomer R(+)[31].

**3.2 Immunological properties**

Thalidomide is able to modify inflammatory processes and to modulate immune reactions [51]. Many data, sometimes contradictory, are available about the immunomodulating action of
thalidomide at the cellular and molecular levels both in vivo and in vitro. Thalidomide’s effects are clearly different from corticoids, ciclosporine, FK506 or phosphodiesterases inhibitors such as pentoxifylline [25]. Thalidomide seems to have both an inhibiting and stimulating action on different cellular immunity effectors. These dichotomous actions may in part be explained by the recently recognized ability of thalidomide to act as a T-cell co-stimulant under certain circumstances. Thalidomide has an inhibiting effect on mononuclear cells by decreasing their chemotactism and phagocytosis capacities [44]. The lymphocytic proliferation induced by allogenic, superantigenic or mitogenic stimulations is inhibited by thalidomide, with an additive effect by ciclosporine A [44, 52, 53]. Furthermore, thalidomide modulates the balance between the different classes of lymphocytes. In vitro studies show that the CD8+ cytotoxic response is stimulated compared to the CD4+ response [54]. An increased CD4+/CD8+ ratio was found in the blood and the cutaneous lesions of patients with erythema nodosum leprosum (ENL). A inversion of this ratio was observed in some of these patients treated by thalidomide [55], which could be one of thalidomide’s effects in ENL. Moreover, thalidomide acts in vitro by skipping the Th1 lymphocyte response towards a Th2 type [56]. Thalidomide has been shown to enhance production of interleukin (IL) 4 and IL5, promoting the shift from a Th1 to a Th2 cytokine pattern. This effect could be of interest in various pathologies associated with a dysregulation of lymphocyte subpopulations [57].

One of the most significant properties of thalidomide is its inhibition of TNF-α synthesis by activated human monocytes [30]. The mechanism by which thalidomide suppresses TNF-α remains unclear. It appears to enhance the degradation of TNF-α mRNA [58] and could interact with two intracellular glycoproteins with anti-TNF-α properties [43]. This anti-TNF-α activity was confirmed in vivo in patients with ENL, tuberculosis, and in HIV infected patients [59]. However, contradictory results were obtained both in vitro and in vivo for the anti-TNF-α properties of thalidomide. Recent data demonstrate that thalidomide may exert a bidirectional dose-dependent effect on TNF-α production, depending on cell type and method of cellular activation. Thus, under certain experimental circumstances, TNF-α production is significantly enhanced by thalidomide in vitro [60]. Furthermore, increased levels of TNF-α in serum have been observed in patients with toxic epidermal necrolysis treated with thalidomide [61]. It is noteworthy that in this double-blind, placebo-controlled trial, treatment with thalidomide was associated with an increased mortality. Increased levels of TNF-α were also observed among HIV-infected patients treated by thalidomide for oral ulcerations [62].
More recently, thalidomide has been shown to inhibit NF-kappa B activation, an ubiquitous transcription factor of central importance in the response of the host to inflammatory stimuli, through suppressing I-kappa B kinase activity [51, 63]. Together, these data suggest that thalidomide has a complex action on the immune system: in conditions characterized by monocyte/macrophage activation and high circulating concentrations of TNF-α, such as ENL, the use of thalidomide to inhibit production of TNF-α may be beneficial. However, in diseases where T-cell activation contributes to the pathogenic process, further T-cell stimulation by thalidomide may be detrimental and result in clinical deterioration [64].

3.3 Anti-angiogenic properties

Anti-angiogenic property of thalidomide was first shown in vivo in a rabbit cornea model [65]. This property is distinct from the anti-TNF-α action [32], and is probably responsible for the teratogenic effect [66]. The inhibition of neovascularisation induced by thalidomide is mediated by inhibition of angiogenic factors such as the vascular endothelial growth factor (VEGF) [67] and basic fibroblast growth factor (bFGF) [68]. At a molecular level, thalidomide, or a breakdown product of thalidomide, could decrease the transcription efficiency of genes related to those angiogenic factors by specifically intercalating into their promoter sites [66]. This inhibition requires metabolic activation, which is species-dependent [69]. These metabolites can be formed in both humans and rabbits, but not in some species of rodents in which thalidomide has no antiangiogenic or teratogenic effects [69].

The anti-angiogenic activity of thalidomide seems particularly interesting in the treatment of malignancies, where angiogenesis has been shown to play an important role [70, 71]. In experimental models of tumor and metastases, thalidomide has been shown to induce an intratumoral hypoxia, to reduce tumor blood vessel density and tumor growth, and to decrease the risk of metastases [72, 73].

4- Clinical applications

Thalidomide has been used in several cutaneous inflammatory disorders. Its efficiency has been proved in erythema nodosum leprosum, severe aphthosis- isolated (figure 2), in Behçet disease- or associated with HIV infection, Jessner-Kanoff’s lymphocytic infiltration, resistant cutaneous lupus, and chronic graft-versus-host reactions. Some other dermatological indications may be of interest, such as prurigo, HIV infection, cutaneous sarcoidosis, chronic or recurrent erythema multiform (figure 3), and pseudo-lymphomas, or numerous other inflammatory dermatoses in single case reports [44, 74-76]. Surprisingly, thalidomide is not efficient in psoriasis [77] and in contrary, exacerbation of psoriasis have been observed with thalidomide [78, 79], illustrating the complexity
of this molecule, since some paradoxal elevation of TNF have also been observed in some patients with toxic epidermal necrolysis [61] or HIV infection [62]. For a more precise description of clinical applications of thalidomide in dermatology, see appendix 2: Laffitte E, Revuz J. Thalidomide. Ann Dermatol Venereol. 2000;127:603-13.

Thalidomide has been used in Kaposi’s sarcoma, with inconstant results [80-82]. Together, these results suggest that thalidomide is not a major therapy for KS, with disappointing response rate and limitations due to side effects, although it could be useful in some specific cases [83]. For an editorial on Thalidomide for Kaposi sarcoma, see appendix 3: Laffitte E. Thalidomide in Kaposi sarcoma: promising or disappointing? Dermatology. 2007;215:171-2.

Considering the good results obtained with the new biologic anti-TNFα compounds, the indication for the use of thalidomide in other inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis or inflammatory bowel diseases are still under debate [84].

Thalidomide has been shown to be an active and promising anti-carcinogenic agent, as a single agent or in combination with dexamethasone or other chemotherapeutic agents, in hematological malignancy, such as relapsing or refractory multiple myeloma, myelodysplasia or acute myeloid leukemia (well reviewed in [70, 85]), and also in solid tumor such as malignant glioma, prostatic, colorectal or renal cell carcinoma [70]. The best response rates have been observed with relapsing or refractory multiple myeloma, ranging from 25 to 69% [85]. Thalidomide could be of interest in cancer cachexia and for distressing night sweats in advanced malignant disease [86, 87]. The dosage and length of treatment are different in inflammatory and neoplastic diseases. A daily dose of 200 mg or less is usually enough to control erythema nodosum leprosum, severe aphtosis or cutaneous lupus, and the dose can progressively be reduced, while in malignancy, thalidomide is started at 200 mg/d an progressively increased to 400-800 mg/d for several months [70, 85].
**Figure 2**: A 18-year old male patient with severe oral aphthosis. He was suffering for severe and relapsing oral aphthosis since he was 9 years old, unresponsive to oral steroids. When he was 13, he consulted in our clinic; and we started a therapy with thalidomide, 50 mg daily with a dramatic improvement in 7 days.

Unfortunately, the aphthosis always recurred when the dose was lower than 25 mg twice a week, and after 5 years of therapy, he developed a sensitive neuropathy. The thalidomide had to be discontinued, and the aphthosis relapsed, without any response to colchicine.
**Figure 3:** a case of recurrent erythema multiform in a 25-year old woman, resistant to several month of high dose oral corticotherapy: see painful ulceration of the tongue and oral mucosae

After one week of thalidomide, 50 mg/day: dramatic improvement of all the lesions
5- Side effects

Thalidomide’s side effects are listed in table 1, Appendix 1. As the number of patients receiving thalidomide for longer periods of time and higher dosages increases (in particular for relapsing multiple myeloma or in HIV patients), several previously unrecognized or underestimated adverse effects have recently been observed. Some side effects can be considered as major and may have serious consequences (teratogenicity, peripheral neuropathy and deep venous thrombosis). Some side effects are usually considered minor, as they tend to appear at the beginning of treatment and generally disappear after dose tapering. However, they may act as serious dose limiting factors or lead to treatment interruption when thalidomide is used in higher dosages as an anticarcinogenic agent (in particular somnolence, constipation and rash). The incidence of each side effect is not accurately known and tends to vary in different studies, depending on the disease and the administered dose of thalidomide.

5.1 Toxicity

The acute toxicity of thalidomide is so low that the toxicological studies made in the Fifties in rodents failed to show lethality, even when in excess of 10,000 mg/kg [25]. Accidental or voluntary overdosing never had any serious consequences, even for amounts of 14 grams [44].

5.2 Major side effects

5.2.1 Teratogenic Effect

The discovery of the teratogenic properties of thalidomide was a surprise, since premarketing animal studies, only performed in rats [25], did not detect it. Later studies showed that rats or mice are species less sensitive to teratogenic effect of thalidomide [88, 89].

The major susceptibility of the human embryo seems to be between the 27th and the 50th day after conception, and a single dose of 100 mg is enough to cause harm [90]. The frequency of malformations after in utero exposure has been estimated in a range of 15 to 100%. The most frequent fetal abnormalities seen in humans are limb defects (75% of the cases), but other abnormalities such as craniofacial abnormalities, malformations of internal organs and central skeletal abnormalities have been observed [26].

The specific mechanism of this embryopathy is not clear yet, and is probably complex with 24 potential mechanisms of action listed [91]. The most recent data suggest that the embryotoxic activity could be related to the formation, under the effect of the prostaglandin H-synthetase, a species-dependent enzyme, of a teratogenic metabolite. This metabolite could induce the production of free radicals responsible for DNA oxidation in the embryonic cells [92]. The anti-angiogenic properties of thalidomide may also play a role in teratogenesis [66].
There is a potential risk of teratogenic effect of thalidomide in treated male, as the molecule is distributed into semen. Congenital malformations have been observed in rabbit’s newborn resulting from breeding experiments with males having a prolonged intake of thalidomide. [45]. Such an effect has not been described in humans yet, but since thalidomide is distributed into human semen after oral dosing, there could be a potential risk in treated male patients [46].

The teratogenic effect is currently well controlled in Western countries with the delivery of the product being restricted by specific control programs (the S.T.E.P.S program and its equivalent in Europe, the Pharmion Management Risk Program, P.R.M.P) to patients using effective methods of contraception, and women managed by repeated pregnancy tests. This is not true everywhere in the world, and at least 34 cases of embryopathy after exposure to thalidomide have been reported in South American lepromatous endemic areas since 1965 [93].

Nevertheless, one should notice that some other highly teratogenic molecules are frequently prescribed by dermatologists, such as isotretinoin. It has been demonstrated that approximately 25 to 30 percent of fetuses exposed to isotretinoin have birth defects [94], which makes isotretinoin as embryotoxic as thalidomide. There are some specific birth control programs associated with isotretinoin use, such as the S.M.A.R.T program in the United States [95], which are not as heavy or expensive as the S.T.E.P.S program.


The possibility of a mutagenic effect was raised in 1994 by McBride (who had described the teratogenic effect in 1961) following two observations of limb malformations in children born to fathers with thalidomide embryopathy [96]. The imputability of thalidomide in the two cases observed was low, and more than 350 victims of thalidomide indexed in England had normal children [97-99]. However, large studies were performed in human and other animals, indicating that thalidomide was devoid of mutagenic activity [100, 101].

5.2.2 Peripheral Neuropathy

As teratogenicity of thalidomide can be controlled by appropriate contraceptive methods, the neurotoxicity of the drug is now one of the main factors limiting its use for a prolonged period [44, 102], especially in cutaneous inflammatory disorders. The exact mechanism of thalidomide-induced neuropathy is still unknown. An individual susceptibility has been suggested, but no correlation with the genetic differences in drug metabolism has been found [103]. Thalidomide neuropathy is known to be an axonal, bilateral, and symmetrical polyneuropathy, mainly sensory, and particularly involving distal extremities. Clinical manifestations of thalidomide-induced neuropathy consist mainly of symmetrical distal painful paresthesia with or without sensory loss in the lower limbs.
Electrophysiologic findings are those of a sensory axonal polyneuropathy with reduction of sensory nerve action potential (SNAP) amplitude and relative conservation of nerve conduction velocities [104]. A 50% decrease of sural SNAP amplitude has been reported to be the best electrophysiologic criterion, SNAP amplitude being closely related to the clinical sensory signs and symptoms [104, 105].

The prevalence of thalidomide-induced neuropathy has been variously estimated in retrospective studies, from less than 1% in 34 patients treated for lepra reactions [106] to more than 70% in small series of patients (four to eight) treated for prurigo nodularis [107-109]. A prevalence of 25% was reported in a series of 60 patients treated for discoid lupus erythematosus during a 2 years period (400 mg per day, then 50-100 mg per day) [110]. In a retrospective study of 42 patients, a prevalence rate of definite thalidomide neuropathy of 21% [111] was observed. In recent series of patients with refractory multiple myeloma treated with high doses of thalidomide, i.e. 200-800 mg per day, neuropathy was reported to occur in 10% to 30% of treated patients [112, 113], but the clinical and electrophysiologic criteria for neuropathy were not clearly specified. This variability in prevalence has been interpreted as reflecting a disease-related susceptibility. In fact the retrospective nature of the studies, the large range of daily doses used, and the heterogeneity of the clinical and electrophysiologic criteria considered for the diagnosis of neuropathy preclude a real estimation of the prevalence rate and risk factors of thalidomide neuropathy. Thalidomide-induced neuropathy was recently prospectively evaluated among 135 patients treated for various dermatologic diseases for 2 years [114]. Definite neuropathy (i.e. electrical plus clinical signs) was present in 25% of the patients but clinical or electrophysiologic evidence of a thalidomide-induced neuropathy were present in 56% of the patients. The incidence rate was maximal during the first year of treatment (20%). The risk of neuropathy was related to the daily dose whatever the duration of treatment and the risk seemed to be negligible for doses less than 25 mg per day, whatever the duration of therapy. After peripheral neuropathy develops, it resolves slowly and is sometimes irreversible [111, 115, 116]. In a follow-up of thalidomide-induced neuropathy over 4 to 6 years, approximately 25% of patients had a full recovery, 25% had a slow improvement, and 50% had persistent sensory symptoms [111, 115, 116]. In a few patients, recovery did not begin for years. Sural nerve biopsies showed severe degeneration of large axons with little sign of regeneration. In other patients, electrophysiologic abnormalities worsened after discontinuation of thalidomide [104]. The use of thalidomide every other day, alternate weeks, or for brief monthly courses has been suggested to minimize the risk of polyneuropathy. However, no studies of these alternative courses have been performed.

It is recommended that a baseline nerve conduction study should be performed in all patients who receive thalidomide within 3 months of initiating therapy, and then repeated every 6 months.
thereafter [114]. If nerve conduction amplitudes are decreased by more than 30% from baseline, more frequent testing is recommended [105]. Thalidomide should be discontinued if nerve conduction amplitudes are decreased by 50% or more. Thalidomide therapy can be cautiously restarted after symptoms of neuropathy resolve [102].

5.2.3 Thalidomide and thromboses
As the use of thalidomide expands, the higher incidence of deep-vein thrombosis (DVT) or pulmonary embolism has been recently reported among patients receiving thalidomide in combination with glucocorticoids or multiagent chemotherapy for multiple myeloma, myelodysplastic syndromes or various carcinomas [117]. The reported rates of these events varied from 0 to 43% of treated patients and occurred at a mean of 2 months after the introduction of thalidomide treatment. Ten cases have been reported in patients taking thalidomide for inflammatory dermatoses, such as lupus or aphthous stomatitis [118-122]. All of these patients had different predisposing factors, such as antiphospholipid syndrome, trauma or Behçet disease.

In cancer patients DVT were safely treated with anticoagulation and did not necessarily warrant discontinuation of thalidomide [117]. On the other hand, in patients with inflammatory diseases, thrombo-embolic events were particularly severe and extensive even after anticoagulation, and thalidomide had to be discontinued.

There is no clear explanation about the thrombogenic effect of thalidomide, but some hypotheses have been suggested: thalidomide, chemotherapy, and glucocorticoids could increase activation of tissue factor in the plasma membrane of tumor cells by way of apoptosis [123]. This phenomenon could be dose-related, since no case has been recorded during a prospective survey of 170 patients treated with daily doses of 100 mg or lower [114].

Together, clinical data suggest that thalidomide could have a thrombogenic effect for a daily dose higher than 100 mg, in patients with predisposing diseases such as multiple myeloma or solid carcinoma, Behçet disease or antiphospholipid syndrome, and when glucocorticoids or multiagent chemotherapy are associated, and those patients should be carefully monitored when thalidomide is started.

5.3 Minor side effects:
The more usual side effects are neuropsychic, digestive, endocrinological and cutaneous.
- neuropsychic in 33 to 100% of the cases [35]: somnolence (45 to 90%), asthenia, drowsiness, cephalalgias, decreased libido, or depressive syndrome are currently observed. More recently, a reversible dementia was reported [124].
- digestive: constipation (15 to 50%), weight gain (30%), xerostomia, abdominal pain and nauseas may occur frequently. A severe hepatic toxicity has been reported once [125].

- endocrinological disorders: several studies in the 1950s and 1960s reported the effects of thalidomide on the endocrine system. More recently, hypothyroidism and significant increases in serum TSH levels have been found after 2 to 6 months in 20% to 74% of patients treated with thalidomide for multiple myeloma [126]. Thalidomide therapy can result in constipation, fatigue, lack of energy and bradycardia, but those signs may also be manifestations of hypothyroidism, and the authors recommend assessment of serum TSH levels before starting thalidomide and every 3 months afterwards, or if the diagnosis of hypothyroidism is suspected. Secondary amenorrhea has been reported in ten women treated with thalidomide for aphtosis or lupus [127-130]. The amenorrhea occurred after 4 to 7 months following the beginning of the treatment, and resolved after the discontinuation of thalidomide. Reintroduction of thalidomide in two patients again induced amenorrhea. Increased FSH and LH levels with low estradiol levels were consistent with a menopausal profile, suggesting a peripheral action rather than central.

- cutaneous side effects: various dermatologic side effects of thalidomide have been reported, but recently with the use of higher dosage their prevalence appear to be higher than previously expected [131, 132]. Skin eruptions have been noted in 46% of myeloma patients taking thalidomide alone or in combination with dexamethasone [131]. Cutaneous side-effects are also more common in HIV-infected patients treated with thalidomide compared to non-infected individuals treated with the drug. In a series of 56 HIV-infected patients treated with thalidomide for 14-21 days, 27% ceased thalidomide because of cutaneous side-effects [132]. The more immunosuppressed the HIV-infected individual was, the more likely they were to experience side-effects. These eruptions can be minor to moderate such as morbilliform or maculopapular rash, but severe skin reaction (DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) [133], exfoliative erythroderma [134], erythema multiform or toxic epidermal necrolysis [131, 135]) have been observed.

6- Guidelines for the clinical use of Thalidomide

Thalidomide is currently available only on special access schemes that differ from country to country. Clinical use is restricted to severe disabling conditions that cause an unacceptable interference with normal life, and only after other treatments have been tried and failed. Approval is usually on an individual patient basis. Thalidomide is prescribed in an off-label setting in most countries. In France, thalidomide has been approved since February, 1997 for erythema nodosum leprosum, Jessner-Kanoff’s lymphocytic infiltration, resistant cutaneous lupus, chronic graft-versus-host reactions, severe aphtosis either isolated or associated with Behçet disease and HIV infection,
and more recently resistant multiple myeloma. In the US, thalidomide has been approved since July, 1998 for erythema nodosum leprosum.

Thalidomide is available as capsules of 50 mg. Until 2008 it was distributed in Europe by Pharmion, which had a monopole of the distribution in Europe. Since 2008, the CELGENE company bought Pharmion laboratories, and now distributes Thalidomide (and that its derivative, lenalidomide) in the entire world. To prevent pregnancy under thalidomide, an extremely strict control program as been established since 2004, the Pharmion Risk Management Program (PRMP) (except France), similar to the U.S. Program (STEPS), which has been previously described and published [136]. This program requires an extensive infrastructure, is time-consuming and requires laborious inputs from prescriber, patient and pharmacist. As a consequence, the price of the drug has increased 400 per cent now with a price of approximately 14 Euros for a 50 mg capsule (2.52 Euros before 2003).

Before treatment, patients must be informed of the risks associated, side effects, and the nature of any alternative treatments using registered drugs. Patients should be in a position to make informed consent and be given a detailed information sheet about the drug. In women of childbearing age, pregnancy should be excluded with a negative test prior to prescribing. If hormonal contraceptives are the chosen means of preventing pregnancy while taking thalidomide, the hormones should be taken for at least 1 month prior to commencing thalidomide. Men taking thalidomide should be advised to wear condoms during sexual intercourse as thalidomide has been detected in semen. Clinical neurological examination and electrophysiological measurements are to be recorded when treatment is started. Risk factors for thrombo-embolism should be recorded, and TSH levels should be determined.

During treatment, pregnancy tests and clinical neurological examinations should be performed monthly. Monthly and electrophysiological measurements every 6 months must be performed. Patients must be educated about the symptoms of peripheral neuropathy and instructed to consult their doctor for electrophysiological testing in the event that such symptoms appear.

After cessation of thalidomide, pregnancy should be avoided for one month in women, and condoms should be continued for 3 months in men (corresponding to a spermatogenesis cycle).
7- Thalidomide on internet
Several websites can be consulted on the net:

- The Thalidomide Victims Association of Canada. URL Address: http://www.thalidomide.ca

- US Food and Drug Administration/Center for Drug Evaluation and Research. The information presented on this page includes consumer and patient information, thalidomide advisory committee and workshop transcripts, the approved labeling text and the medical review on which the decision to approve this drug was based. Also included are selected links to other web sites containing thalidomide information.
  URL Address: http://www.fda.gov/cder/news/thalinfo

- Thalidomide: potential benefits and risk, open public scientific workshop, convened on September 9 and 10, 1997, by the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC)
  URL Address: http://www.fda.gov/oashi/aids/thalexe.html

8- The future? Thalidomide derivatives and lenalidomide in dermatology

  8.1 Lenalidomide: the second generation imid
With the “rediscovery” of thalidomide, several structural analogues have been developed in an attempt to find compounds with thalidomide’s immunomodulatory properties without the associated side effects [137, 138]. Preliminary results from human studies in vitro and in vivo have shown some of these compounds to be clinically effective with reduced toxicity, but they are still under investigation [139, 140]. In particular, lenalidomide (Revlimid®), a second-generation thalidomide derivative has been extensively studied (figure 1). Lenalidomide was identified as more potent than thalidomide and devoid of many of the serious adverse reactions associated with thalidomide administration, such as neuropathy [141] or teratogenicity (in rabbit) [142]. Many potential mechanisms of action exist for lenalidomide, including inhibition of angiogenesis, enhancement of immune system function, inhibition of tumor stromal cell interactions, and blockade of actions of various cytokines [141].
There is appreciable clinical activity of this drug in hematologic malignancies including myelodysplastic syndrome, multiple myeloma, and chronic lymphocytic leukemia (CLL).
8.2 Lenalidomide in dermatology

In dermatology, there are only anecdotal reports of lenalidomide use: an oral aphthosis was cleared with 10 mg/d of lenalidomide in a patient with Behçet disease [143] but was complicated by a deep venous thrombosis, and good clinical response was obtained in two patient with resistant discoid lupus erythematosus [144]. In 15 patients with cutaneous T-cell lymphoma receiving 25 mg of lenalidomide daily for 21 days of a 28-day cycle, 5 patients have achieved a partial response and 6 patients have experienced minor responses such as regression of cutaneous tumor lesions, improved lymphadenopathy, and skin improvement [145]. However, the actual extremely high price of this drug (8789.00 CHF for 21 capsules of 25 mg), which is even higher than the current TNF inhibitors (cf infra) will probably not contribute to his prescription for non hematologic diseases.

Some cutaneous side effects have been described in up to 30 % of the patient with lenalidomide given for hematological malignancy, with mild to moderate morbilliform or urticarial rash, which did not require the discontinuation of the drug [144]. More severe reaction have been reported: two cases of acute neutrophilic dermatoses suggesting Sweet syndrome [146, 147], and 12 reports of Stevens Johnson syndrome, three reports of erythema multiform and one report of toxic epidermal necrolysis among approximately 57,000 patients who received lenalidomide from market launch on December 2005 through June 2008 [148].

8.3 Our experience with lenalidomide in cutaneous disorders

We have recently treated two patients with lenalidomide that was given by Celgene Company as compassionate use:

- One patient followed for a disfiguring non Langerhans-cell cutaneous histiocytosis, type xanthoma disseminatum of Montgommery, with a doubtful association with a low-grade cutaneous T cell lymphoma. After three cycles of 15 mg/days during the first 21 days of a 28-day cycle, there was no clinical response and the patient experienced side effects as a cutaneous rash following the second cycle and abdominal pain with diarrhea.

- A patient suffering for a severe scleromyxedema associated with a benign monoclonal gammopathy since 7 years. According to the literature, intravenous immunoglobulin and thalidomide are therapeutic options [148, 149]. This patient had already had 3 infusions of immunoglobulin several years ago, with only a partial response, and was suffering for a bilateral Carpal tunnel syndrome which is a compression of the median nerve at the wrist, that was a relative contra-indication to thalidomide. As the disease was related to the monoclonal gammopathy, we used the dose of Revlimid we would use to treat a myeloma, i.e. 25 mg/d during the first 21 days of a 28-day cycle. After two cycles, a slight clinical response was observed.
Part III

The new era: Biologics as Tumor Necrosis Factor antagonists

1- Introduction

The discovery of the major role of TNF in the physiopathology of certain inflammatory diseases and notably in rheumatoid arthritis and Crohn's disease has led to the emergence of new anti-TNF drugs [8, 9]. The anti-TNF currently available are etanercept, a fusion protein composed of a soluble TNF alpha receptor, infliximab, a chimeric monoclonal antibody and adalimumab, a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to TNF [13]. These new therapeutic arms issued from bio-technology, so-called biological therapies (biologics) have rapidly demonstrated their efficacy in the treatment of various inflammatory diseases [10, 11]. In particular, these drugs have revolutionized the treatment of psoriasis and may benefit for other cutaneous diseases, such as granulomatous diseases, Behçet’s disease or hidradenitis suppurativa [10, 11].

However, these promising new treatments, although expensive, and with yet unknown long term side effects, justify rigorous assessment of their efficacy and tolerance in each indication. We will discuss the role of these anti-TNF biologics in psoriasis and other cutaneous diseases, and highlight some side effects specific to dermatology, the other side effects of anti-TNF have been extensively described in several reviews [11, 150-153].

2- TNF antagonists used in dermatology: Etanercept, Infliximab Adalimumab (figure 1)

2.1 Etanercept

Etanercept (Enbrel®) is a recombinant human TNF-receptor fusion protein that antagonizes the effects of endogenous TNF by competitively inhibiting its interaction with cell-surface receptors [149]. Etanercept is composed by 2 molecules of the extracellular domains of the p75 TNF receptor and the constant fragment of IgG1. In vitro analyses indicate a reduced stability of etanercept-TNF complexes compared with infliximab-TNF complexes as well as a remaining biologic activity of TNF released from the etanercept-TNF complexes. Although etanercept contains the Fc portion of IgG1, it does not appear to fix the complement. It is also speculated that, because of the different binding properties of etanercept compared with infliximab, the former is unlikely to form
aggregates on the surface of TNF-producing cells that can activate complement-dependent lysis and antibody-dependent cell-mediated cytotoxicity [150]. Adalimumab and infliximab induce apoptosis of activated cultured peripheral monocytes and cells presenting the transmembrane form of TNF, whereas etanercept does not. In humans, higher avidity and better stability of membrane-bound TNF was demonstrated with anti-TNF mAb (infliximab and adalimumab) than with etanercept, which leads to more efficient apoptosis [151]. This difference in reverse signalling attributable to a difference in membrane-bound TNF targeting may have other consequences. For example, anti-tuberculosis–specific T cells show a clear difference in effector function. Two in vitro studies provided the same results: adjunctive infliximab or adalimumab treatment to specific human anti-tuberculosis T cells was much more efficient in decreasing proliferation and interferon-gamma secretion by these T cells than was adjunctive etanercept treatment [151, 152]. These data suggest that adalimumab and infliximab have a better ability for granuloma disruption than etanercept. This may explain the lower efficacy of etanercept in granulomatous diseases such as Crohn’s disease or sarcoidosis (cf infra), but also a lower risk for granulomatous infections such as tuberculosis [153]. In Switzerland, etanercept is approved for the treatment of rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, ankylosing spondylarthritis, and chronic plaque psoriasis after failure of phototherapy, and systemic treatment such as methotrexate or ciclosporine. Etanercept is applied in the therapy of plaque psoriasis subcutaneously (SC) at a dose of 25 mg twice weekly for cycles of 24 weeks only. For the first 12 weeks of treatment, the dosage may be doubled to 50 mg twice weekly.

### 2.2 Infliximab

Infliximab (Remicade®) is a chimeric monoclonal antibody [149]. The variable regions are of murine origin and are coupled to human IgG1 and κ Fc domains. Infliximab binds to all forms of soluble and membrane-bound TNF with high specificity. The ability of infliximab to bind to membrane-bound TNF appears to be linked to additional effects on TNF–producing cells (apoptosis, complement lysis, antibody-dependent cellular cytotoxicity), which have been described in vitro and in vivo [154] and have been proposed to contribute to the clinical efficacy of the drug.

Infliximab (Remicade®) is administered as a short intravenous infusion over at least 2 hours at a total dose of 5 mg/kg body weight. According to the label for plaque psoriasis, infusions are given at weeks 0, 2, and 6 at the beginning and then every 8 weeks for maintenance therapy. In psoriasis, infliximab is indicated for monotherapy, whereas in rheumatologic conditions, infliximab is often used in combination with methotrexate, a regimen that has not been investigated systematically in psoriasis yet. In Switzerland, infliximab is approved for the treatment of rheumatoid and psoriatic
arthritis, ankylosing spondylarthritis, Crohn's disease, and chronic plaque psoriasis after failure of phototherapy, systemic treatment such as methotrexate, and after etanercept and adalimumab.

2.3 Adalimumab

Adalimumab (Humira®) is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to TNF [149]. Like infliximab, adalimumab neutralizes the biologic activities of TNF by blocking its interactions with the p55 and p75 cell surface receptors, thus modulating TNF-dependent biologic responses. Binding properties of adalimumab are similar to those of infliximab. Less is known about the ability of adalimumab to induce cell-depleting effects, but based on structural similarities to infliximab, it is conceivable that adalimumab may induce apoptosis, complement lysis, and antibody dependent cellular cytotoxicity.

Adalimumab is applied for plaque psoriasis as monotherapy at a dose of subcutaneously 40 mg eow after a loading dose of 80 mg at week 0.

In Switzerland, infliximab is approved for the treatment of rheumatoid and psoriatic arthritis, ankylosing spondylarthritis, Crohn's disease, and chronic plaque psoriasis after failure of phototherapy, systemic treatment such as methotrexate or cyclosporine.

**Figure 1:** Mechanism of anti-TNF biologics. Etanercept is a recombinant human TNF-receptor fusion protein that antagonizes the effects of soluble TNF (sol TNF) while Infliximab and Adalimumab are monoclonal antibodies that bind to all forms of soluble and transmembrane TNF.
3- TNF antagonists in psoriasis

Treatment strategies for psoriasis include topical treatments, phototherapy, and systemic therapies including methotrexate, cyclosporine, acitretin and biologic agents [155]. Patients with mild disease may benefit from topical agents and phototherapy. Systemic treatments are limited to patients with moderate-to-severe psoriasis in whom the activity of skin lesions and concurrent symptoms cannot be sufficiently controlled with topical treatments and with phototherapy. Since 2000, moderate to severe plaque psoriasis has been identified as a target disease by the pharmaceutical industry for the development of anti-TNF agents. Several big and well-designed clinical studies, with hundreds of patients have been performed, showing the efficacy of these drugs, with an acceptable tolerance profile. Noteworthy, TNF inhibitors have been much better studied in psoriasis than the classical (and much less expensive) systemic therapies, methotrexate and cyclosporine. In the meantime, several epidemiological studies were done in an attempt to prove that psoriasis was a disease severe enough to justify the extremely high cost of these new drugs.

3.1 Identification of psoriasis as a severe disease; cost of illness in Switzerland
Psoriasis is a disease affecting approximately 2% to 3% of the population in Western countries [156]. Among several clinical phenotypes chronic plaque-psoriasis is most frequent and accounts for about 90% of cases [156]. Psoriasis may cause substantial problems in everyday life with significant impairment of quality of life [157], and several studies suggested that patients with severe psoriasis have an increased risk for cardiovascular disease, depressive illness, and a decreased life expectancy [159-163]. Currently incurable, psoriasis causes remarkable direct costs, work limitations and productivity loss [164-166].

In 2007, we have participated to a Swiss study initiated in order to estimate the impact of psoriasis in terms of resources used, associated costs, and quality of life impairment. We concluded that moderate-to-severe psoriasis is associated with significant impact on quality of life and at least 4-fold higher costs than mild psoriasis, indicating need for efficient control of the disease. This cost-of-illness study provides specific health economic data for further healthcare decision making, particularly with the advent of new therapeutic agents for effective psoriasis control.


3.2 Treating chronic plaque psoriasis with biologics
The three TNF inhibitors used in psoriasis, etanercept, infliximab and more recently adalimumab have been evaluated as monotherapy for chronic plaque psoriasis. Some tools have been used to evaluate and compare their efficacy: the Body Surface Area (BSA), the Physican Global Assessment (PGA) and the more precise Psoriasis Area and Severity Index (PASI) which evaluate
the erythema, infiltration, desquamation and surface of the psoriatic lesion. Clinical improvement is measured by the percentage change in PASI score, and drug approval often depends on a 50% improvement in the baseline PASI score, also known as a PASI 50; but the main objective is the PASI 75 after 12 or 24 weeks, which reflect a significant improvement of the disease [158]. Several clinical trials have been performed since 2000 with etanercept, infliximab or adalimumab; the results of these trials are well summarized in different recent reviews [149, 155, 159, 160]. Most of these trials are not comparative, but are testing the drug against placebo. There is no head to head comparative study with the different TNF inhibitors, and it is difficult to rank these drugs according efficacy in plaque psoriasis. However, infliximab is remarkable for the rapidity of clinical response. At week 10-12, infliximab (5 mg/kg) seems to be slightly more effective than adalimumab (40 mg/eow), and more effective than etanercept (100 mg/w) and etanercept (50 mg/w) with 75 to 80%, 71 to 79%, 49% and 34% of patients achieving PASI 75, respectively [170-175]. Only one recent trial compares adalimumab to methotrexate (15 to 22.5 mg/w), which obtains 35% of patients achieving PASI75 [174].

Some long term data are now available, suggesting that there could be a lost of efficacy, at least for infliximab when used in monotherapy and in an intermittent schedule, and etanercept which is more efficient when used 50 mg BIW compare to 25 mg BIW [161]. For these three drugs, a long term use in a continuous way is probably more efficient than an intermittent therapy.

3.3 Treating other forms of psoriasis with biologics

TNF inhibitors have been used with success in other form of psoriasis: psoriatic arthritis [149], erythrodermic [162], generalized pustular psoriasis [163], recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease) [164] acrodermatitis continua of Hallopeau [165] and nail psoriasis [173].


There are also some data suggesting that antiTNF can be use in patients with chronic C hepatitis.


3.4 Practical use in Switzerland

In Switzerland, the first TNF inhibitor reimbursed by health insurances for plaque psoriasis was etanercept in 2006, followed by adalimumab in 2008 and infliximab in 2009. Given the high cost of these drugs compare to classical therapies (Figure 2), there are some obvious prescription restriction by health authorities. Etanercept and adalimumab are approved for moderate to chronic
plaque psoriasis (with a definition of BSA>10 or PASI >10) after failure or contra-indication of phototherapy, and systemic treatment such as acitretin, methotrexate or ciclosporine. Infliximab is approved after failure of etanercept or adalimumab. CF table 1 for a synoptic view of TNF inhibitors use in Switzerland.

Figure 2: Comparative cost of one year of therapy for chronic plaque psoriasis. Price are in Swiss francs.

* For infliximab, price indicated is for the drug only, excluding the infusion cost
<table>
<thead>
<tr>
<th>Agent</th>
<th>Anti-TNF-α</th>
<th>Anti-IL.12/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nom générique</td>
<td>Enbrel®</td>
<td>Remicade®</td>
</tr>
<tr>
<td>Molécule</td>
<td>Etanercept ETA</td>
<td>Infliximab IFX</td>
</tr>
<tr>
<td>Fabricant</td>
<td>Wyeth / Pfizer</td>
<td>Centocor / Essex</td>
</tr>
<tr>
<td>Mécanisme d'action</td>
<td>Protéine de fusion recombinante du récepteur du TNFα, se liant à la forme soluble et membranaire du TNF-α.</td>
<td>Anticorps monoclonal chimérique IgG1 se liant à la forme soluble et membranaire du TNF-α.</td>
</tr>
<tr>
<td>Garantie SVK</td>
<td>oui</td>
<td>oui</td>
</tr>
<tr>
<td>Forme d’administration</td>
<td>Seringue pré-remplie (25, 50mg)</td>
<td>Poudre lyophilisée pour injection intraveineuse (2 heures)</td>
</tr>
<tr>
<td>Bilan initial</td>
<td>FSC, ASAT/ALAT, CRP, HBs-Ag, HBs-Ac, HCV-Screening, HIV, Quantiferontest, Rx thorax f/p. β-HCG urinaire.</td>
<td>FSC, ASAT/ALAT, CRP, HBs-Ag, HBs-Ac, HBC-Ac, HCV-Screening, HIV, Quantiferontest, Rx thorax f/p. Chez la femme en âge de procréer: β-HCG urinaire, contraception jusqu’à 6 mois après</td>
</tr>
<tr>
<td>Voie d’administration</td>
<td>s.c.</td>
<td>i.v.</td>
</tr>
<tr>
<td>Dosage</td>
<td>2x25mg/sem ou 1x50mg/sem. En cas d’atteinte sévère ou d’obésité: 2x50mg/sem pendant 12 sem. 0,8mg/kg/sem en</td>
<td>5mg/kg @ sem 0,2,6, puis toutes les 8 sem. Traitement combiné avec MTX low-dose (10 mg/sem) recommandé.</td>
</tr>
<tr>
<td>Latence moyenne d’effet</td>
<td>4-8 sem</td>
<td>1-4 sem</td>
</tr>
<tr>
<td>PASI 75 : (comparaison directe n’est pas possible car il n’y pas étude comparative)</td>
<td>Sem 12: 34% (2x25mg) / 49% (2x50mg). Sem 24 adultes: 44%(2x25mg), 71% (1x50mg)</td>
<td>75-80% (sem 10)</td>
</tr>
<tr>
<td>Coût:</td>
<td>2 x 25mg ou 1 x 50mg: 25’711 CHF / an (seulement médicament pour poids de 60-80kg)</td>
<td>26750-35’667 CHF / an</td>
</tr>
<tr>
<td>Fenêtre thérapeutique</td>
<td>oui</td>
<td>non</td>
</tr>
<tr>
<td>Intervalle de monitoring:</td>
<td>Aucun selon Compendium. Mois 1, M 3, puis tous les 3 M</td>
<td>@ sem 2 avant perfusion, @ sem 6 avant perfusion puis toutes les 8 sem</td>
</tr>
<tr>
<td>Suivi biologique</td>
<td>FSC, CRP, ASAT/ALAT (max 3x limite sup.)</td>
<td>FSC, CRP, ASAT/ALAT (max 3x N)</td>
</tr>
<tr>
<td>Suivi clinique:</td>
<td>PASI</td>
<td>PASI</td>
</tr>
<tr>
<td>Anticorps neutralisants</td>
<td>6%, pas de perte d'efficacité possible.</td>
<td>23.3%, perte d'efficacité possible.</td>
</tr>
<tr>
<td>Agent</td>
<td><strong>Enbrel®</strong></td>
<td><strong>Remicade®</strong></td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
</tr>
<tr>
<td><strong>Contre-indications:</strong></td>
<td>Insuffisance cardiaque NYHA III-IV, grossesse et allaitement, infection, vaccins vivants. Néoplasie, maladie démyélisante (y compris familiale), maladies autoimmunes.</td>
<td>Insuffisance cardiaque NYHA III-IV, grossesse et allaitement, infection, vaccins vivants, cytopénie, hépatopathie, néoplasie, maladie démyélisante (y compris familiale), maladies autoimmunes. Allergie aux anticorps murins.</td>
</tr>
<tr>
<td><strong>Effets indésirables</strong> (liste non exhaustive, non triés par ordre de fréquence, imputabilité pas nécessairement prouvée)</td>
<td>Réactions au site d'injection (par ex. érythème, démangeaison en cas d'allergie au latex), Infection des voies respiratoires: (pharyngite à streptocoques chez l'enfant), prurit, thrombo-cytopenie, urticaire, angioœdème, lupus, SEP, vasculite, purpura palmoplantaire, exanthème psoriasiforme (1-5%), psoriasis pustuleux, éruption lupus-like, toxidermie.</td>
<td>Infection virale et bactérienne (50% des décès annoncés), fièvre, maladie séricie, maladie autoimmune, lupus-like, cytopénie, céphalées, vertige, exacerbation d'une maladie démyélisante, flush, troubles gastro-intestinaux, hépatopathie, exanthème, prurit, réaction de perfusion (jusqu'à l'anaphylaxie), éruption psoriasiforme, réactivation d'une infection opportuniste, carcinome épidermoïde.</td>
</tr>
<tr>
<td><strong>En cas de HBV</strong></td>
<td>Oui sous Lamivudine 3 mois avant le début du traitement et pendant le traitement, HBV-DNA et tests hépatiques tous les 2 mois (avec gastroentérologue).</td>
<td>Oui sous Lamivudine 3 mois avant le début du traitement et pendant le traitement, HBV-DNA et tests hépatiques tous les 2 mois (avec gastroentérologue).</td>
</tr>
<tr>
<td><strong>En cas de HCV</strong></td>
<td>Oui, contrôler la charge virale après 2 mois, en cas d'augmentation &gt;20%: stop traitement</td>
<td>Oui avec monitoring des fonctions hépatiques et JHCV-RNA, avis d'un gastroentérologue.</td>
</tr>
<tr>
<td><strong>En cas de VIH</strong></td>
<td>En cours d'évaluation, pourrait augmenter CD4</td>
<td>En cours d'évaluation.</td>
</tr>
<tr>
<td><strong>En cas de TB latente</strong></td>
<td>Sous INH et Benadon pendant 9 mois. Traitement possible après 1 mois d'INH.. Le mieux documenté dans cette situation.</td>
<td></td>
</tr>
<tr>
<td><strong>Carcinogénèse</strong></td>
<td>Les inhibiteurs du TNFα n'augmentent pas le risque de néoplasie [166], hormis les tumeurs cutanées épithéliales et ev. les hémopathies</td>
<td></td>
</tr>
</tbody>
</table>
4- Side effects: some dermatological particularities

Although TNF inhibitors are generally well-tolerated, notable side effects have been reported including injection reactions (or infusion reactions for infliximab), a risk of serious infections, including tuberculosis or pneumocystis pneumonia, demyelinating disorders, such as multiple sclerosis or optic neuritis, a possible increased risk of lymphoproliferative malignancies, autoimmune diseases such as cutaneous lupus or lupus like syndrome, vasculitis, rare cases of pancytopenia, aplastic anaemia, and aggravation of congestive heart failure. These “classical” side effects have been extensively described in several reviews [11, 150-153, 196] and we will focus in this work on specific and less often described side effects in dermatology.

4.1 Infections: tuberculosis and tuberculosis screening in psoriasis patients

Anti-TNF treatment increases markedly the risk of reactivating latent tuberculosis (LTBI), but very few data are available in psoriasis patients. We have conducted a study, in which we retrospectively compared the results of the tuberculin skin test (TST) and the T-SPOT.TB interferon gamma release assay (IGRA) to risk factors of LTBI in 50 psoriasis patients before anti-TNF treatment [167]. Ninety percent of the patients had prior vaccination by BCG. T-SPOT.TB was strongly associated with a presumptive diagnosis of LTBI (OR: 7.43; 95% CI 1.38-39.9), which was not the case for the TST. Agreement between T-SPOT.TB and TST was poor $\kappa= 0.33$ (SD: 0.13). LTBI was detected and treated in 20% of the patients. In 20% of the cases, LTBI was not retained in spite of a positive TST in front of a negative T-SPOT.TB. All patients received an anti-TNF for a median of 56 weeks (range: 20-188); among patients with TST+ /T-SPOT.TB-, no tuberculosis was detected with a median follow-up duration of 64 weeks (range: 44-188). One case of disseminated TB occurred after 28 weeks of adalimumab in a patient with LTBI in spite of LTBI treatment with rifampicine. This study is the first to underlines the frequency of LTBI in psoriasis patients (20%), and to support the use of IGRA instead of TST for its detection. Nevertheless, there is still a risk of tuberculosis under anti-TNF even if LTBI is correctly diagnosed and treated.


4.2 Cutaneous inflammatory side effects

Various and unexpected cutaneous side effects have been described with TNF inhibitors in patients treated for rheumatic diseases or Crohn’s disease: eczematiform and atopic dermatitis like eruptions, paradoxal onset of psoriasis with palmoplantar pustulosis, and some other and less frequent cutaneous side effects [196, 198].
4.2.1 Eczematiform and atopic rash

Itchy eczematous rashes or atopic dermatitis-like eruptions have been described with the 3 TNF blockers [198-200]. In all cases, the skin lesions were located primarily on the extremities within the antecubital and popliteal fossae, but also in the face or trunk area (Figure 2). The eruption usually occurs several months after the beginning of the therapy, may improve after cessation of the drug, and switching of anti-TNF is not always associated with recurrence of the eruption. The mechanism of these eruptions is poorly known. It is probably not an allergic reaction to the drug, since these lesions are late, but rather a cytokine imbalance induced by the anti-TNF, leading to the induction of an inflammatory skin reaction resembling to eczema with proTh2 cytokines. Conversely, TNF blockers have been used to treat some severe cases of atopic dermatitis [168].


4.2.2 Palmoplantar pustulosis and paradoxical psoriasis

Currently there are more than 200 reports of patients presenting new-onset and worsening of psoriasis during TNF blockade therapy, well reviewed in [169-171]. Psoriasis occurring during TNF blockade has been mostly reported as the pustular type occurring on the palms and soles (Figure 3), but also generalized. This eruption can occur at any time from days to years after drug initiation but generally after several month of therapy, and some authors suggest that the incidence may be higher in patients treated with adalimumab [203]. This phenomenon has been reported in nearly all diseases treated with TNF antagonists, including psoriasis, rheumatoid arthritis, ankylosing spondylitis, and other seronegative spondylarthritides, including psoriatic arthritis, Behçet’s disease, inflammatory bowel disease, and juvenile idiopathic arthritis. The majority of patients were reported to have an excellent therapeutic response to the drug, with the exception of the unexpected development of psoriatic skin lesions. The evolution of TNF-blockers induced psoriasis is unpredictable: stopping the drug or switching to another agent leads inconstantly to improvement of the eruption.

Despite different mechanisms of action of these agents, the lack of resolution of these cases after switching to a different TNF blocker suggests a TNF class effect. It has been suggested that this paradoxical occurrence of psoriasis with TNF inhibition could be linked to an imbalance between TNF and interferon alpha (IFN) [172, 173]. An indirect relationship exists between TNF levels and regulation and release of IFN, and a pathogenic role of IFN in the development of psoriasis has been shown in murine models and with IFN-treated humans [171]. There is no consensus concerning the treatment of these paradoxical eruptions. Nevertheless, the majority of authors suggest an aggressive treatment of the skin disease with topical steroids and phototherapy before considering a change in the TNF antagonist.
Figure 2: atopic-like dermatitis in a 25 year-old patient, developed after several month of etanercept therapy for rheumatoid arthritis

Figure 3: palmoplantar pustulosis in a 40 year-old patient, developed after 10 month of adalimumab therapy for ankylosing spondylitis
4.2.3 Other inflammatory cutaneous side effects

Several other cutaneous inflammatory disorders have been described: erythema multiform, Steven’s Johnson syndrome, toxic epidermal necrolysis, vasculitis [171], granulomatous diseases such as interstitial granulomatous dermatitis, granuloma annulare or cutaneous sarcoidosis [174], lichenoid eruptions, bullous pemphigoid [175]. Interestingly and conversely, TNF inhibitors have also been reported to be effective in some of these various conditions [12], illustrating the complexity of the immunological mechanisms leading to these inflammatory disorders.

4.3 Skin carcinomas

4.3.1 Melanoma and melanoma skin cancers

In psoriasis patients, there is a well demonstrated increased risk of melanoma and squamous cell carcinoma (SCC) among patients treated by ciclosporine and psoralen-UVA therapy (PUVA) [176, 177]. With the TNF blockers, some observations have been made of induction of eruptive melanoma and benign melanocytic naevi by etanercept and infliximab [178, 179] but also with azathioprine and methotrexate. Furthermore, there have been 9 reports of severe or multiple and eruptive SCC of the skin, 3 reports of SCC of the penis and two reports of multiple basal cell carcinoma under TNF blockers [180-186]. Interestingly, most of the patients had received etanercept for rheumatoid arthritis (8 patients) or psoriasis (4 patients) and psoriatic arthritis (1) and all had signs of cutaneous photodamage or had been previously treated by PUVA and Methotrexate. The rapidity of onset of these SCC in at risk patients suggests that TNF blockers could facilitate the revelation of preclinical SCC.

A large observational study of patients with rheumatoid arthritis demonstrated an increased risk for the development of nonmelanoma skin cancer (odds ratio 1.5, 95% confidence interval 1.2-1.8) and a trend toward increased risk of melanoma (odds ratio 2.3, 95% confidence interval 0.9-5.4) in patients treated with biologic agents (largely the 3 TNF inhibitors) [187]. A large-scale cohort study observed the incidence of NMSC in patients with RA using TNF blockers versus a control group of patients with non-inflammatory osteoarthritis [188]. Among the 15,789 patients with RA, the authors found that TNF antagonists displayed an increased risk of NMSC when prescribed either alone (hazard ratio, 1.24) or in combination with MTX (hazard ratio, 1.97).

These findings contrast with the results of a study including a clinical trials’ database of 1442 RA patients receiving etanercept (4257 patient-years) and a postmarketing database of more than 125 000 patients receiving commercial etanercept (>250 000 patient-years) [189], in which no association was found with an increase in the incidence of cutaneous SCC.

Taking together, these data and observations suggest that, as for other immunosuppressive drugs, TNF blockers may increase the risk SCC in subjects with risk factors (sun exposure, high amounts
of PUVA). However, long term follow-up studies are still lacking to evaluate this risk in psoriasis patients.

4.3.2 Cutaneous lymphoma
Aggressive cutaneous T-cell lymphomas have been reported after etanercept, adalimumab and infliximab treatment [190-193]. Most of these cases were remarkable for the sudden onset and rapid progression of disease. This atypical disease progression suggests that patients may have had a pre-existing T-cell lymphoma kept in check by cellular immunity. Then anti-TNF therapy may have lifted this control and thus permitted development of the T-cell clone. Currently, these cases are rare, and no convincing evidence exists to prove that patients treated with anti-TNF have a higher risk of cutaneous lymphoma than the general population.

5- TNF antagonists in other cutaneous diseases
The clinical efficacy of TNF blockers has been reported in various inflammatory skin diseases, well reviewed in [12]. We will focus on several cutaneous diseases of peculiar interest.

5.1 Cutaneous sarcoidosis
Cutaneous sarcoidosis is a dermatosis characterized by noncaseating granulomatous infiltration. Standard therapeutic options include corticoids, antimalarials, methotrexate (monotherapy or combination) and newer therapies including pentoxifylline, tetracyclines, isotretinoin, leflunomide, thalidomide, chlorambucil, melatonin, cyclosporine A, allopurinol, laser surgery and medium-dose UVA1 phototherapy [194]. Nevertheless, cutaneous sarcoidosis is often a refractory chronic disease and aggressive therapy may be required. The mechanisms underlying the formation, maintenance, and spontaneous resolution of the sarcoid granuloma are not well understood but there are several pieces of evidence that TNF plays a crucial role [16]. Several case reports and small series have reported the efficacy of different anti-TNF agents in refractory cutaneous and systemic sarcoidosis [195-200]. Adalimumab and infliximab induce apoptosis of cells presenting the bound form of TNF [201], whereas etanercept does not. These data suggest that adalimumab and infliximab have a better ability to disrupt granuloma than etanercept. There are clinical pieces of evidence to support this hypothesis, with a better activity of adalimumab and infliximab than etanercept in granulomatous disorders such as sarcoidosis and Crohn’s disease. Moreover, paradoxical development of noncaseating granuloma has been documented under anti-TNF agents and more frequently with etanercept, raising the hypothesis that TNF inhibitors may sometimes leave sufficient cytokine activation to support granuloma formation [202-205].

The optimal modalities and dosing regimen of TNF blockers in cutaneous granulomatosis has still to be defined. We have reported the case of a patient with refractory cutaneous sarcoidosis in whom
anti-TNF agents were ineffective at the standard dosage, but who responded to dose escalation (Figure 4).


5.2 Necrobiosis lipoidica

Necrobiosis lipoidica is an uncommon granulomatous skin disease of non infectious origin. It is often associated with diabetes and its high morbidity is due to chronicity and eventually ulceration. Clinically atrophic pretibial plaques are surrounded by an erythematous infiltrated border and histology shows palissading granulomatous inflammation affecting the entire dermis. Therapeutic options are numerous: a non exhaustive list consists of topical or intralesional steroids, topical tacrolimus, photochemotherapy, antimalaric drugs, photodynamic therapy (PDT), fumaric acid, thalidomide, pentoxifylline, heparin injections and excision followed by graft [206]. None of them is constantly effective and all have been used off-label without any comparative study.

Three reports have already described the efficacy of systemic infliximab in necrobiosis lipoidica [207, 208]. To avoid systemic side effects considering it is a cutaneous local disease, we have conducted a prospective study of intralesional injection of infliximab (Barde C, Thielen AM, Campanelli A, Laffitte E, Saurat J-H. Intralesional infliximab in non infectious cutaneous granulomas: three cases of necrobiosis lipoidica. Arch Dermatol 2009, submitted). Three patients with necrobiosis lipoidica were treated with over one year. The lesions diminished significantly in all the patients (Figure 5). In one patient the injections relieved pain and the remission lasted for as long as one and a half years but a recurrence was observed in the two other cases.

Intralesional injections of infliximab have been used in Crohn’s diseases and in rheumatoid arthritis [209-211], but this is the first report of intralesional injections of infliximab in dermatology. It is a safe therapeutic option avoiding potential serious side effects of intravenous infliximab. The long follow up of the patients showed that it is a suspensive treatment.
**Figure 4:** Cutaneous sarcoidosis of the left cheek. Excellent evolution 7 months after adalimumab treatment initiation at a dosage of 80 mg every other week

**Figure 5:** Necrobiosis lipoidica lesion before and 6 month after local injections of infliximab
5.3 Hidradenitis suppurativa
Hidradenitis suppurativa (HS) is a chronic relapsing skin disorder characterized by recurrent inflammatory lesions leading in later stages to sclerosis, sinus tract formation, and fistula formation [212]. A number of treatment options are available for HS, including antibiotics, retinoids, immunosuppressants, and surgery. Despite such treatments, HS causes significant morbidity. The etiopathogenesis of HS remains incompletely understood, but the most relevant pathological finding in HS is an inflammatory process with or without overlapping infection. An increasing number of reports have been published on the use of TNF antagonists in refractory HS and this disease could be identified as another target disease by the pharmaceutical industry for the development of anti-TNF agents in dermatology. However, most of these reports are small retrospective or prospective series of patients, and lengths of follow-up of most reported cases of HS that were treated with anti-TNF agents were short [213-217].

5.4 Behçet’s disease and aphtosis
Behçet’s disease is a chronic inflammatory multisystem disease, and presumably occurs as a result of a vasculitis. Aphtha of the mucous membrane and cutaneous ulcers and/or papulopustules are amongst the main symptoms of this disease and are useful parameters for the clinical determination of activity. In addition, the eyes, CNS, gastrointestinal tract and joints are often involved. In an acute attack of Behçet’s disease, raised TNF serum levels can be detected. Because of the chronic course of the disease and the occasionally poor therapeutic response, clinical trials with TNF blockers have been carried out, extensively reviewed in [12]. Dramatic therapeutic response has been obtained with TNF blockers in patients with orogenital ulcerations, nodular lesions, papulopustular lesions, attacks of arthritis and uveitis [245, 246].

5.5 Netherton syndrome
Netherton syndrome (NS) is a skin disorder caused by mutations in SPINK5, a gene encoding the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI). It has been recently shown that the pro-Th2 cytokine thymic stromal lymphopoeitin (TSLP) and pro-inflammatory cytokines such as TNF are overexpressed in LEKTI deficient epidermis [24].
We have reported the case of a 25-year old woman with NS, confirmed by the absence of LEKTI expression in the epidermis and mutation in SPINK5. She presented with recurrent severe inflammatory flares with focal blistering, unresponsive to therapy with systemic dapsone, topical steroids, tacrolimus and pimecrolimus. Following an induction phase (week 0-2-6), maintenance therapy with infliximab was given at 5mg/kg every other month. A dramatic improvement was
NS is a genodermatosis caused by the absence of LEKTI protein, which induces a loss of the stratum corneum due to hyperactivity of epidermal proteases. The inflammatory skin reaction associated leading to eczema is poorly understood. TSLP is a cytokine produced by epithelial cells, including keratinocytes, which drives the inflammatory response toward a Th-2 type [218, 219] and whose role in asthma and atopic dermatitis is being increasingly identified.

In our observation, high levels of TSLP in skin were correlated to the activity of inflammatory disease, which is consistent with recent data [24] and indicates that this cytokine seems important in Netherton syndrome. The significant and prolonged improvement of the eruption with infliximab suggests that TNF could play a crucial role in Netherton's syndrome and in the inflammatory cascade mediated by TSLP. Our data suggest that an anti-TNF should be considered as a valuable therapeutic approach for NS.


6- Perspectives for TNF antagonists

Two main lines of development are to be expected with TNF inhibitors. Firstly the establishment of national and international registries of patients, in order to assess their effectiveness and tolerance independently from the pharmaceutical industry, and secondly the emergence of new molecules inhibiting TNF.

6.1 Independent evaluation of efficacy and safety: usefulness of registries

With the licensing of the first TNF inhibitors, independent academia-initiated but industry-sponsored drug registers were set up by the national rheumatology societies in several European countries in order to monitor the long-term safety and effectiveness of this new generation of drugs
In contrast to the patients in a registry who receive care in the natural clinical setting, subjects in randomized clinical trials are selected according to study criteria and may therefore not reflect the experience of patients in clinical practice. It is possible that particular risks and opportunities in the real patient population may therefore go undetected in randomized clinical trials. Moreover, with an increasing number of new drugs and multiple exposures of individual patients the assignment of events to specific treatments has become exceedingly difficult. Major data on drug safety with regard to infections - tuberculosis as a major example [153, 221], malignancies, cardiovascular events, pregnancy outcomes and deaths have been obtain from these registries [220].

In the light of the increased risk of infections and malignancies in rheumatoid arthritis patients treated with anti-tumor necrosis factor antibodies, the production of reliable data for psoriasis is essential, and the importance of this industry-independent way of obtaining data has been also identified in Dermatology [222]. Following this concept, nine European countries have established registries to collect data on systemic psoriasis treatment (Italy, Sweden, Spain, Germany, Israel, France, United Kingdom, The Netherlands and Portugal) [223]. The main objectives of these registers are to assess the long-term safety and effectiveness of systemic psoriasis treatments and to identify target phenotypes that may allow for specific, individualized treatments. Even though different in some respects of study design and monitoring, these registers share a number of common features: they include all licensed biological agents, they observe the patients for a defined period of time or indefinitely irrespective of the drug given and they use comparator cohorts or national registers in order to put the results into perspective. Moreover, there have been some initiatives to combine the results from these national registries into compatible international databases to increase their power and impact [223, 224]. In Switzerland such an effort has been done, with the creation of the Swiss Dermatology Network for Biologics (SDNB) which includes representatives of the different Swiss clinics of Dermatology, and whose goal is to establish a Swiss register of biologics.

Several informations have already been obtained from these national registries: data on current prescription behaviour for the treatment of psoriasis in private practices in Germany [225], long term efficacy and tolerability of etanercept in daily practice in The Netherlands [226], and a significant and unexpected number of abnormalities of liver function in UK [227].

The question of skin malignancy being precipitated by biologic therapy will only be answered by large well-designed cohort studies, which will collect data over the medium to long term on patients treated with these drugs. Clearly this is of major importance in a cohort of patients with psoriasis because treatment history will often include photochemotherapy potentially predisposing to melanoma and nonmelanoma skin cancer.
6.2 Development of other targeted TNF inhibitors

Since the success of anti-TNF biological agents, much effort has gone into developing other drugs. Some are new and more targeted biologics (solTNF inhibitors), or small molecule, orally bioavailable TNF inhibitor (TACE inhibitors and p38MAP Kinase inhibitors). Another approach is to induce an active anti-TNF immunotherapy (TNF Kinoid). There is few data in human yet, and these drugs have been mostly used in patients with rheumatoid arthritis (RA). But Dermatology may benefit in a short future of these new ways of TNF inhibition.

6.2.1 solTNF inhibitors

Because mouse models show that inhibition of soluble TNF (solTNF) is anti-inflammatory, while inhibition of transmembrane TNF (tmTNF) sensitizes to infection and exacerbates demyelinating diseases, multiple groups are attempting to develop soluble TNF-selective antagonists [8]. For example, a group from Geneva presented data showing that a solTNF-selective ‘dominant-negative’ TNF biologic (XPro11595) consisting of blocking solTNF while sparing tmTNF was as anti-inflammatory as etanercept in a mouse arthritis model without suppressing normal innate immunity to listeriosis or tuberculosis [228]. Another group described development of selective antagonists of the TNFR1 receptor, including ‘R1antTNF’, a pegylated variant of TNF which blocks TNFR1 signalling but preserves signalling of tmTNF through TNFR2, which was as efficacious as etanercept in a mouse arthritis model, yet safer in mice challenged with adenovirus infection [229].

6.2.2 TACE inhibitors and p38MAP Kinase inhibitors

One of the ways to block TNF actions in the body is to inhibit the processing of pro-TNF by blocking TNF-alpha converting enzyme (TACE). This target has been validated in preclinical trials for the treatment of RA. Many compounds belonging to different chemical classes have been synthesized as selective TACE inhibitors. Although there is a growing concern among scientific fraternity whether a TACE inhibitor would show a favourable pharmacological profile and can be recommended for treating RA; there are many promising TACE inhibitors in the preclinical studies [230].

Another way is to target p38 mitogen-activated protein (MAP) kinase. This kinase occupies a central role in the regulation of IL-1beta and TNF-alpha signalling network at both the transcriptional and translational level. Since the mid-1990s, an immense number of inhibitors of p38 MAP kinase have been characterised in vitro, and to date several compounds have been advanced into clinical trials. Based on very promising preclinical data, a number of pharmaceutical companies have developed inhibitors of MAP kinase p38 that predominantly impact its alpha subunit. Most of the therapeutics are in phase II clinical trials; the therapeutic effects have not yet reached expectations [231].
6.2.3 TNF Kinoid
As an alternative to anti-human TNF monoclonal antibodies and other TNF blocker approved drugs, an active anti-TNF immunotherapy as been developed, based on a vaccine comprised of a keyhole limpet hemocyanin-TNF heterocomplex immunogen, namely TNF Kinoid (TNF-K) adjuvanted in incomplete Freund’s adjuvant [232]. In mice transgenic for TNF (TTg mice) which spontaneously develop arthritides, TNF Kinoid vaccination elicited high titers of antibodies that neutralized TNF bioactivities. Moreover, in this mouse model, anti-TNF immunotherapy with TNF-K had a sustained, but reversible therapeutic efficacy, supporting the potential suitability of this approach in treating human disease [233]. Human studies are ongoing in RA and Crohn’s diseases with promising results, but no published data are available yet.
Conclusions

Even if thalidomide and anti-TNF “biologics” are TNF inhibitors, their effect and side effects are completely different; these drugs are complementary and useful drugs in dermatology.

Thalidomide is a powerful molecule with convenient oral administration which represents a significant therapeutic option in various immunological disorders and oncology. Its use requires assessing the risk-benefit ratio depending on the indication as this ratio varies according to country. The main side effects can be minimized by selecting suitable patients (in particular identifying thromboembolic and neuropathy risk factors) and carefully following published recommendations [234]. Teratogenicity can be controlled through effective contraceptive methods, as with other highly teratogenic molecules frequently prescribed, for example isotretinoine in acne.

Given the uniqueness and complexity of the mechanisms of action, which are not fully understood yet, new and unexpected indications could arise in the future, like chronic heart failure or bleeding angiodysplasias, as recently reported [235-237]. The development of thalidomide derivatives with fewer side effects is promising, but it is not clear yet if dermatology will benefit from these new drugs.

The “biologics” TNF inhibitors have opened a new realm of therapy for patients with psoriasis. They have also displayed utility in many other inflammatory dermatoses. Their side effect profile, lack of end organ toxicity, and lack of interaction with other medications, make them an excellent therapeutic option for many patients, but as with any systemic immunosuppressant medication they must be monitored appropriately. However, the use of TNF blockers is limited by high costs. Cost and insurance reimbursement may therefore limit the availability of these drugs for some patients, especially in off label cases. Moreover, there is still a need of collecting long term safety data, and creation of industry-independent cohorts and national registers should be promoted.
References


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Appendix
Appendix 1

Thalidomide: an old drug with new clinical applications

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Thalidomide has several targets and mechanisms of action: a hypnosedative effect, several immunomodulatory properties with an effect on the production of TNF-α and the balance between the different lymphocyte subsets and an antiangiogenic action. Thalidomide has been used in several cutaneous inflammatory disorders (e.g., erythema nodosum leprosum in lepromatous leprosy, cutaneous lupus erythematosus and severe aphthosis), cancers (e.g., relapsed/refractory multiple myeloma, malignant melanoma and systemic signs in cancer) and inflammatory conditions (e.g., Crohn’s disease and rheumatoid arthritis). Several side effects are associated with thalidomide. Some are major, such as teratogenicity, peripheral neuropathy and deep vein thrombosis. Somnolence and rash are frequently reported when thalidomide is used at higher doses as an anticarcinogenic agent and can lead to dose reduction or treatment discontinuation depending on severity. Minor side effects include abdominal pain and endocrine disturbances. To prevent the teratogenicity, use of thalidomide is strictly controlled in western countries with close adherence to a birth control programme. Close monitoring for early development of peripheral neuropathy is also recommended.

Keywords: cutaneous inflammatory disorders, deep vein thrombosis (DVT), peripheral neuropathy, relapsed/refractory multiple myeloma, teratogenicity, thalidomide, TNF-α


1. Introduction

Thalidomide was first synthesised in 1954 by the German pharmaceutical firm Chemie Grüenthal, and was marketed in Europe in October 1957 as an antiemetic and non-barbiturate sedative hypnotic [1]. The first pharmacological studies performed on rodents showed a fast sedative effect and remarkably low toxicity even at high doses. Between 1957 and 1961, thalidomide was widely used by pregnant women for its antiemetic effect in the treatment of morning sickness [2]. A significant teratogenic effect of thalidomide was reported in 1961 [3] after a rise in reported cases of phocomelia, a previously rare congenital malformation. Almost 6000 cases of internal or external deformities were attributed to thalidomide during this period [2,4] and the drug was withdrawn from the market. In 1965, a dramatic improvement of erythema nodosum leprosum (ENL) treated with thalidomide was reported by Sheskin [5], and the discovery in 1991 of thalidomide’s anti-TNF-α activity [6] led to renewed interest in this drug. Since then, this anti-TNF-α effect has been studied, with several clinical indications under investigation. There are two main avenues of current research: immunomodulatory action in various inflammatory diseases and antiangiogenic action, which seems to be of interest in oncology.
2. Pharmacology

Thalidomide, or \( \alpha-(N\text{-pthalimido})\)-glutarimide, is a glutamic acid derivative. The molecule is a racemic mixture of the \((S)\) and \((R)\) enantiomers. There is some evidence to suggest that the two enantiomers act differentially: the \((R)\) enantiomer could be responsible for the sedative effect [7], whilst the \((S)\) enantiomer could have the immunomodulatory, antiangiogenic [8] and teratogenic properties, although this hypothesis is debatable [9]. However, in humans, this difference is not relevant since chiral interconversion between the two enantiomers in vivo leads to a racemic mixture in 2 h [10]. The solubility of this lipophilic molecule is low in water and alcohol and the molecule is sensitive to hydrolysis at a pH of > 6 [11,12].

The pharmacokinetics of thalidomide have been studied both in humans and animals [12-15]. After oral absorption in healthy volunteers, the peak plasma concentration is reached in 3.2 ± 1.4 – 4.39 ± 1.27 h (\(T_{\text{max}}\)) [12,13]; this is delayed by consumption of a high-fat meal [16]. The apparent volume of distribution (\(V_d\)) is very broad, 120 l [14], with a rapid penetration of the haematoencephalic and placental barriers [17]. Animal studies have shown that thalidomide is distributed in all tissues, with a predilection for the digestive tract and the kidneys [18].

The principal metabolic pathway is probably non-enzymatic hydrolysis, leading to at least 12 breakdown products, some of which could have their own pharmacological activity [19]. Hydroxylated products have also been detected, suggesting that enzymes from the cytochrome P450 family with a predilection for the digestive tract and the kidneys [18].

Thalidomide is a glutamic acid derivative. The molecule is a racemic mixture of the \((S)\) and \((R)\) enantiomers related to the \(\alpha\)-\((N\text{-pthalimido})\)-glutarimide, is a glutamic acid derivative. The molecule is a racemic mixture of the \((S)\) and \((R)\) enantiomers. There is some evidence to suggest that the two enantiomers act differentially: the \((R)\) enantiomer could be responsible for the sedative effect [7], whilst the \((S)\) enantiomer could have the immunomodulatory, antiangiogenic [8] and teratogenic properties, although this hypothesis is debatable [9]. However, in humans, this difference is not relevant since chiral interconversion between the two enantiomers in vivo leads to a racemic mixture in 2 h [10]. The solubility of this lipophilic molecule is low in water and alcohol and the molecule is sensitive to hydrolysis at a pH of > 6 [11,12].

The pharmacokinetics of thalidomide have been studied both in humans and animals [12-15]. After oral absorption in healthy volunteers, the peak plasma concentration is reached in 3.2 ± 1.4 – 4.39 ± 1.27 h (\(T_{\text{max}}\)) [12,13]; this is delayed by consumption of a high-fat meal [16]. The apparent volume of distribution (\(V_d\)) is very broad, 120 l [14], with a rapid penetration of the haematoencephalic and placental barriers [17]. Animal studies have shown that thalidomide is distributed in all tissues, with a predilection for the digestive tract and the kidneys [18].

The principal metabolic pathway is probably non-enzymatic hydrolysis, leading to at least 12 breakdown products, some of which could have their own pharmacological activity [19]. Hydroxylated products have also been detected, suggesting that enzymes from the cytochrome P450 family could be involved [20].

Excretion of thalidomide and its metabolites is mainly via the kidneys. The plasma half-life ranges from 6.17 ± 2.56 to 8.70 ± 4.11 h [12-14]. Excretion of thalidomide in semen was studied in rabbits. After two oral doses separated by 18 h, thalidomide was found in semen from the 6th hour until the 12th day. Thalidomide was not only spent in Phase I [26]. This sedative action is preferentially related to the \((R)\) enantiomer [7].

Thalidomide seems to have both inhibitory and stimulatory actions on different cellular immunity effectors. These dichotomous actions may, in part, be explained by the recently recognised ability of thalidomide to act as a T cell co-stimulant under certain circumstances. Thalidomide has an inhibitory effect on mononuclear cells by decreasing their chemotactic and phagocytic capacities [20]. The lymphocytic proliferation induced by allergenic, superantigenic or mitogenic stimulation is inhibited by thalidomide, with an additive effect by cyclosporin A [20,28,29]. Furthermore, thalidomide modulates the balance between the different classes of lymphocytes. In vitro studies show that the CD8⁺ cytotoxic response is stimulated compared to the CD4⁺ response [30]. An increased CD4⁺/CD8⁺ ratio was found in the blood and the cutaneous lesions of patients with ENL. An inversion of this ratio was observed in some of these patients treated with thalidomide [31], which could be one of thalidomide’s effects in ENL. Moreover, thalidomide acts in vitro by skipping the T₄₁ lymphocyte response towards a T₄₂ type [32]. Thalidomide has been shown to enhance production of IL-4 and -5, promoting the shift from a T₄₁ to a T₄₂ cytokine pattern. This effect could be of interest in various pathologies associated with dysregulation of lymphocyte subpopulations [33].

One of the most significant properties of thalidomide is its inhibition of TNF-α synthesis by activated human monocytes [6]. The mechanism by which thalidomide suppresses TNF-α remains unclear. It appears to enhance the degradation of TNF-α mRNA [54] and could interact with two intracellular glycoproteins with anti-TNF-α properties [19]. This anti-TNF-α activity was confirmed in vivo in patients with ENL, tuberculosis and in HIV-infected patients [35]. However, contradictory results were obtained both in vitro and in vivo for the anti-TNF-α properties of thalidomide. Recent data demonstrate that thalidomide may exert a bidirectional

3. Biological properties

3.1 Hypnosedative action

Thalidomide acts by a different mechanism to barbiturates, possibly involving activation of sleep centres that depend on GABA receptors [14]. The effect of thalidomide on sleep is very particular, and differs from all other hypnotic drugs by increasing the time spent in Phases 3–4 and REM (rapid eye movement) and decreasing the time spent in Phase I [26]. This sedative action is preferentially related to the \((R)\) enantiomer [7].

3.2 Immunological properties

Thalidomide is able to modify inflammatory processes and modulate immune reactions [27]. There is an abundance of data, sometimes contradictory, available concerning the immunomodulatory action of thalidomide at the cellular and molecular levels both in vivo and in vitro. Thalidomide’s effects are clearly different from corticoids, cyclosporin, FK-506, and phosphodiesterase inhibitors such as pentoxifylline [1].

Thalidomide seems to have both inhibitory and stimulatory actions on different cellular immunity effectors. These dichotomous actions may, in part, be explained by the recently recognised ability of thalidomide to act as a T cell co-stimulant under certain circumstances. Thalidomide has an inhibitory effect on mononuclear cells by decreasing their chemotactic and phagocytic capacities [20]. The lymphocytic proliferation induced by allergenic, superantigenic or mitogenic stimulation is inhibited by thalidomide, with an additive effect by cyclosporin A [20,28,29]. Furthermore, thalidomide modulates the balance between the different classes of lymphocytes. In vitro studies show that the CD8⁺ cytotoxic response is stimulated compared to the CD4⁺ response [30]. An increased CD4⁺/CD8⁺ ratio was found in the blood and the cutaneous lesions of patients with ENL. An inversion of this ratio was observed in some of these patients treated with thalidomide [31], which could be one of thalidomide’s effects in ENL. Moreover, thalidomide acts in vitro by skipping the T₄₁ lymphocyte response towards a T₄₂ type [32]. Thalidomide has been shown to enhance production of IL-4 and -5, promoting the shift from a T₄₁ to a T₄₂ cytokine pattern. This effect could be of interest in various pathologies associated with dysregulation of lymphocyte subpopulations [33].

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dose-dependent effect on TNF-α production, depending on cell type and method of cellular activation. Thus, under certain experimental conditions, TNF-α production is significantly enhanced by thalidomide in vitro [36]. Furthermore, increased levels of TNF-α in serum have been observed in patients with toxic epidermal necrolysis treated with thalidomide [37]. It is noteworthy that in this double-blind, placebo-controlled trial, treatment with thalidomide was associated with increased mortality. Increased levels of TNF-α were also observed among HIV-infected patients treated with thalidomide for oral ulcerations [38].

More recently, thalidomide has been shown to inhibit NF-κB activation, a ubiquitous transcription factor of utmost importance in the response of the host to inflammatory stimuli, through suppression of inhibitor κ B (I-κB) kinase activity [27,39].

Together, these data suggest that thalidomide has a complex action on the immune system: in conditions characterised by monocyte/macrophage activation and high circulating concentrations of TNF-α, such as ENL, the use of thalidomide to inhibit production of TNF-α may be beneficial. However, in diseases where T cell activation contributes to the pathogenic process, further T cell stimulation by thalidomide may be detrimental and result in clinical deterioration [40].

3.3 Antiangiogenic properties
The antiangiogenic properties of thalidomide were first demonstrated in vivo in a rabbit cornea model [41]. This property is distinct from the anti-TNF-α action [8] and is probably responsible for the teratogenic effects [42]. The inhibition of neovascularisation induced by thalidomide is mediated by inhibition of angiogenic factors such as vascular endothelial growth factor (VEGF) [43] and basic fibroblast growth factor (bFGF) [44]. At a molecular level, thalidomide, or a breakdown product of thalidomide, could decrease the transcription efficiency of genes related to those angiogenic factors by specifically intercalating into their promoter sites [42]. This inhibition requires metabolic activation, which is species-dependent [45]. These metabolites can be formed in both humans and rabbits but not in some species of rodents in which thalidomide has no antiangiogenic or teratogenic effects [45].

The antiangiogenic activity of thalidomide seems particularly interesting in the treatment of malignancies, where angiogenesis has been shown to play an important role [46,47]. In experimental models of tumours and metastases, thalidomide has been shown to induce an intratumoural hypoxia, to reduce tumour blood vessel density and tumour growth, and to decrease the risk of metastases [48,49].

4. Thalidomide derivatives
With the ‘rediscovery’ of thalidomide, several structural analogues have been developed in an attempt to discover compounds with thalidomide’s immunomodulatory properties without the associated side effects [50,51]. Preliminary results from human studies in vitro and in vivo have shown some of these compounds to be clinically effective with reduced toxicity, but they are still under investigation [52,53].

5. Clinical applications
Thalidomide has been used in several cutaneous inflammatory disorders. Its efficiency has been proven in ENL, severe aphthosis (either isolated or associated with Behçet’s disease or HIV infection), Jessner–Kanoff lymphocytic infiltration, resistant cutaneous lupus, and chronic graft-versus-host reactions. Some other dermatological indications may be of interest, such as prurigo, HIV infection, cutaneous sarcoidosis, chronic or recurrent erythema multiforme, pseudolymphomas, and numerous other inflammatory dermatoses in single case reports [20,54-56]. Considering the good results obtained with the new biological anti-TNF-α compounds, the use of thalidomide in other inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis or inflammatory bowel diseases, is still under debate [57].

Thalidomide has been shown to be an active and promising anticarcinogenic agent, both as a single agent or in combination with dexamethasone or other chemotherapeutic agents, in haematological malignancy, such as relapsing or refractory multiple myeloma, myelodysplasia or acute myeloid leukaemia (reviewed well in [46,58]), and also in solid tumours such as malignant glioma, prostatic, colorectal or renal cell carcinoma [46]. The best response rates have been observed with relapsing or refractory multiple myeloma, ranging 25 – 69% [58]. Thalidomide could be of interest in cancer cachexia and for distressing night sweats in advanced malignant disease [59,60].

The dosage and duration of treatment differ in inflammatory and neoplastic diseases. A daily dose of ≤ 200 mg is usually enough to control ENL, severe aphthosis or cutaneous lupus, and the dose can progressively be reduced, whilst in malignancy, thalidomide is started at 200 mg/day and progressively increased to 400 – 800 mg/day for several months [46,58].

6. Side effects
Thalidomide’s side effects are listed in Box 1. As the number of patients receiving thalidomide for longer periods of time and at higher doses increases (in particular, for relapsing multiple myeloma or in HIV patients), several previously unrecognised or underestimated adverse effects have recently been observed. Some side effects can be considered as major and may have serious consequences (teratogenicity, peripheral neuropathy and deep vein thrombosis [DVT]). Some side effects are usually considered minor, as they tend to appear at the beginning of treatment and generally disappear after dose tapering. However, they may act as serious dose-limiting factors or lead to treatment interruption when thalidomide is used at higher doses as an anticarcinogenic agent (in particular, somnolence, constipation and rash). The incidence of each side effect is not accurately known and tends to vary in different studies, depending on the disease and the administered dose of thalidomide.
Thalidomide: an old drug with new clinical applications

6.1 Toxicity

The acute toxicity of thalidomide is so low that the toxicological studies conducted in rodents in the 1950s failed to show lethality, even when at doses in excess of 10,000 mg/kg [1]. Accidental or voluntary overdosing never had any serious consequences, even for doses of 14 g [20].

6.2 Major side effects

6.2.1 Teratogenic effects

The discovery of the teratogenic properties of thalidomide was a surprise, since premarketing animal studies, only performed in rats [1], did not detect it. Later studies showed that rats and mice are less sensitive to the teratogenic effects of thalidomide [61,62].

The major susceptibility of the human embryo to the effects of thalidomide seems to occur between 27 and 50 days after conception; a single dose of 100 mg is enough to cause harm [63]. The frequency of malformations after in utero exposure has been estimated to be in the range 15–100%. The most frequent fetal abnormalities seen in humans are limb defects (75% of the cases) but other abnormalities such as craniofacial abnormalities, malformations of internal organs and central skeletal abnormalities have been observed [2].

The specific mechanism of this embryopathy is not yet clear and is probably complex, with 24 potential mechanisms of action listed [64]. The most recent data suggest that the embryotoxic activity could be related to the formation, under the effect of the prostaglandin H-synthetase, a species-dependent enzyme, of a teratogenic metabolite. This metabolite could induce the production of free radicals responsible for DNA oxidation in the embryonic cells [65]. The antiangiogenic properties of thalidomide may also play a part in teratogenesis [42].

There is a potential risk for teratogenic effects of thalidomide in the treated male, as the molecule is distributed into semen. Congenital malformations have been observed in rabbits born as a result of breeding experiments with males having a prolonged intake of thalidomide [21]. Such an effect has not yet been described in humans, but since thalidomide is distributed into human semen after oral dosing, there could be a potential risk in treated male patients [22].

The teratogenic effects of thalidomide are currently well-controlled in western countries, with the delivery of the product being restricted to patients using effective methods of contraception and women managed by repeated pregnancy tests. This is not true everywhere in the world, and at least 34 cases of embryopathy after exposure to thalidomide have been reported in South American lepromatous endemic areas since 1965 [66].

The possibility of a mutagenic effect was raised in 1994 by McBride (who had described the teratogenic effects in 1961) following two observations of limb malformations in children born to fathers with thalidomide embryopathy [67]. The imputability of thalidomide in the two cases observed was low, and more than 350 victims of thalidomide indexed in England had normal children [68-70]. However, large studies were performed in humans and animals, indicating that thalidomide was devoid of mutagenic activity [71,72].

6.2.2 Peripheral neuropathy

As the teratogenicity of thalidomide can be controlled by appropriate contraceptive methods, the neurotoxicity of the drug is now one of the main factors limiting its use for a prolonged period [20,73], especially in cutaneous inflammatory
disorders. The exact mechanism of thalidomide-induced neuropathy is still unknown. An individual susceptibility has been suggested but no correlation with the genetic differences in drug metabolism has been found [74]. Thalidomide neuropathy is known to be an axonal, bilateral and symmetrical polyneuropathy, mainly sensory and particularly involving distal extremities. Clinical manifestations of thalidomide-induced neuropathy consist mainly of symmetrical distal painful paresthesia with or without sensory loss in the lower limbs [20]. Electrophysiological findings are those of a sensory axonal polyneuropathy with reduction of sensory nerve action potential (SNAP) amplitude and relative conservation of nerve conduction velocities [75]. A 50% decrease of sural SNAP amplitude has been reported to be the best electrophysiological criterion, as SNAP amplitude is closely related to the clinical sensory signs and symptoms [75,76].

Various estimates of the prevalence of thalidomide-induced neuropathy have been made in retrospective studies, from < 1% in 34 patients treated for lepra reactions [77], to > 70% in a small series of patients (four to eight) treated for prurigo nodularis [78-80]. A prevalence of 25% was reported in a series of 60 patients treated for discoid lupus erythematosus over a 2-year period (400 mg/day, followed by 50 – 10 mg/day) [81]. In a retrospective study of 42 patients, a prevalence rate of definite thalidomide neuropathy of 21% [82] was observed. In a recent series of patients with refractory multiple myeloma treated with high doses of thalidomide, i.e., 200 – 800 mg/day, neuropathy was reported to occur in 10 – 30% of treated patients [83,84], but the clinical and electrophysiological criteria for neuropathy were not clearly specified. This variability in prevalence has been interpreted as reflecting a disease-related susceptibility. In fact, the retrospective nature of the studies, the large range of daily doses used and the heterogeneity of the clinical and electrophysiological criteria considered for the diagnosis of neuropathy preclude a real estimation of the prevalence rate and risk factors of thalidomide neuropathy. Thalidomide-induced neuropathy was recently prospectively evaluated among 135 patients treated for various dermatological diseases for 2 years [89]. Definite neuropathy (i.e., electrical plus clinical signs) was present in 25% of the patients, but clinical or electrophysiological evidence of a thalidomide-induced neuropathy were present in 56% of the patients. The incidence rate was maximal during the first year of treatment (20%). The risk of neuropathy was related to the daily dose, whatever the duration of treatment, and the risk seemed to be negligible for doses of < 25 mg/day, whatever the duration of therapy. After peripheral neuropathy develops, it resolves slowly and is sometimes irreversible [82,86,87]. In a follow-up of thalidomide-induced neuropathy over 4 – 6 years, ~ 25% of patients made a full recovery, 25% had a slow improvement and 50% had persistent sensory symptoms [82,86,87]. In a few patients, recovery did not begin for years. Sural nerve biopsies showed severe degeneration of large axons with little sign of regeneration. In other patients, electrophysiological abnormalities worsened after discontinuation of thalidomide [75]. The use of thalidomide every other day, on alternate weeks or for brief monthly courses has been suggested to minimise the risk of polyneuropathy. However, no studies of these alternative courses have been performed.

It is recommended that a baseline nerve conduction study should be performed in all patients who receive thalidomide within 3 months of initiating therapy and then repeated every 6 months thereafter [85]. If nerve conduction amplitudes are decreased by > 30% from baseline, more frequent testing is recommended [76]. Thalidomide should be discontinued if nerve conduction amplitudes are decreased by ≥ 50%. Thalidomide therapy can be cautiously restarted after symptoms of neuropathy resolve [73].

6.2.3 Thalidomide and thromboses

As the use of thalidomide expands, a higher incidence of DVT or pulmonary embolism has been recently reported among patients receiving thalidomide in combination with glucocorticoids or multi-agent chemotherapy for multiple myeloma, myelodysplastic syndromes or various carcinomas [88]. The reported rates of these events varied from 0 to 43% of treated patients and occurred at a mean of 2 months after the introduction of thalidomide treatment. Ten cases have been reported in patients taking thalidomide for inflammatory dermatoses such as lupus or aphthosis nodularis [78-80]. A prevalence of 25% was reported in a series of patients (four to eight) treated for prurigo nodularis [78-80]. A prevalence of 25% was reported in patients treated with daily doses of ≥ 200 mg/day, ≤ 800 mg/day [85]. Together, clinical data suggest that thalidomide could have a thrombogenic effect at a daily dose of > 100 mg in patients with predisposing diseases such as multiple myeloma or solid carcinoma, Behçet’s disease or antiphospholipid syndrome, and when glucocorticoids or multi-agent chemotherapy are associated with thalidomide; all such patients should be carefully monitored when treatment with thalidomide is started.

6.3 Minor side effects

The most common side effects are neuropsychological, digestive, endocrinological and cutaneous.

6.3.1 Neuropsychological

In 33 – 100% of the cases [11], somnolence (45 – 90%), asthenia, drowsiness, cephalgias, decreased libido or depressive
syndrome are currently observed. More recently, a reversible dementia was reported [95].

6.3.2 Digestive
Constipation (15 – 50% of cases), weight gain (30% of cases), xerostomia, abdominal pain, and nausea may occur frequently. Severe hepatic toxicity has once been reported [96].

6.3.3 Endocrinological disorders
Several studies in the 1950s and 60s reported the effects of thalidomide on the endocrine system. More recently, hypothyroidism and significant increases in serum thyroid-stimulating hormone (TSH) levels have been found after 2 – 6 months in 20 – 74% of patients treated with thalidomide for multiple myeloma [97]. Thalidomide therapy can result in constipation, fatigue, lack of energy, and bradycardia, but these signs may also be manifestations of hypothyroidism, and the authors recommend assessment of serum TSH levels before starting thalidomide and every 3 months afterwards or if the diagnosis of hypothyroidism is suspected. Secondary amenorrhoea has been reported in ten women treated with thalidomide for aphthosis [98-101]. The amenorrhoea occurred 4 – 7 months following the start of treatment and resolved after the discontinuation of thalidomide. Re-introduction of thalidomide in two patients again induced amenorrhoea. Increased FSH and luteinisng hormone (LH) levels with low oestradiol levels were consistent with a menopausal profile, suggesting a peripheral rather than central action.

6.3.4 Cutaneous side effects
Various dermatological side effects of thalidomide have been reported, but, recently, with the use of higher doses, their prevalence appears to be higher than previously expected [102,103]. Skin eruptions have been noted in 40% of myeloma patients taking thalidomide alone or in combination with dexamethasone [102]. Cutaneous side effects are also more common in HIV-infected patients treated with thalidomide compared to non-infected individuals treated with the drug. In a series of 56 HIV-infected patients treated with thalidomide for 14 – 21 days, 27% stopped taking thalidomide because of cutaneous side effects [103]. The more immunosuppressed the HIV infected individual, the more likely they were to experience side effects.

These eruptions can be minor-to-moderate, for example, morbilliform or maculopapular rash, but severe skin reactions (drug rash with eosinophilia and systemic symptoms [DRESS] [104], exfoliative erythroderma [105], erythema multiforme or toxic epidermal necrolysis [102,106]) have been observed.

7. Guidelines for the clinical use of thalidomide
Thalidomide is currently available only through special access schemes that differ from country to country. Clinical use is restricted to severe disabling conditions that cause an unacceptable disruption to normal life and only after other treatments have been tried and then subsequently fail. Approval is usually on an individual patient basis. Thalidomide is prescribed in an off-label setting in most countries. In France, thalidomide has been approved since February, 1997 for ENL, Jessner–Kanoff lymphocytic infiltration, resistant cutaneous lupus, chronic graft-versus-host reactions, severe aphthosis either isolated or associated with Behçet’s disease and HIV infection, and, more recently, resistant multiple myeloma. In the US, thalidomide has been approved since July, 1998 for ENL. The US safety programme for thalidomide has been described previously and is published as STEPS® (System for Thalidomide Education and Prescribing Safety) [107].

Before treatment, patients must be informed of the associated risks, side effects and the nature of any alternative treatments using registered drugs. Patients should be in a position to give informed consent and to receive a detailed information sheet about the drug. In women of childbearing age, pregnancy should be excluded with a negative test prior to prescribing. If hormonal contraceptives are the chosen means of preventing pregnancy whilst taking thalidomide, then they should be taken for at least 1 month prior to commencement of thalidomide treatment. Men taking thalidomide should be advised to wear condoms during sexual intercourse, as thalidomide has been detected in semen. Clinical neurological examination and electrophysiological measurements are to be recorded when treatment is started. Risk factors for thromboembolism should be recorded and TSH levels should be determined.

During treatment, pregnancy tests and clinical neurological examinations should be performed monthly and electrophysiological measurements every 6 months. Patients must be educated about the symptoms of peripheral neuropathy and instructed to consult their doctor for electrophysiological testing in the event that such symptoms appear.

After cessation of thalidomide, pregnancy should be avoided for 1 month in women, and condoms should be worn by men for at least 3 months (corresponding to a spermatogenesis cycle).

8. Thalidomide on the net
Several websites can be consulted on the net:

- US FDA/Center for Drug Evaluation and Research (CDER) (http://www.fda.gov/cder/news/thalinfo). The information presented on this page includes consumer and patient information, thalidomide advisory committee and workshop transcripts, the approved labelling text and the medical review on which the decision to approve this drug was based. Also included are selected links to other websites containing information on thalidomide.
• Thalidomide: potential benefits and risks, open public scientific workshop, convened on 9th and 10th September, 1997, organised by the National Institutes of Health (NIH), the FDA and the Centers for Disease Control and Prevention (CDC) (http://www.fda.gov/oashi/aids/thalexc.html).

9. Expert opinion

Thalidomide is a powerful molecule that represents a significant therapeutic option in various immunological disorders and oncology. Its use requires assessing the risk–benefit ratio depending on the indication, as this ratio varies from country to country. The main side effects can be minimised by selecting suitable patients (in particular, identifying thromboembolic and neuropathy risk factors) and carefully following published recommendations[108]. Teratogenicity can be controlled through effective contraceptive methods, as with other highly teratogenic molecules frequently prescribed (e.g., isotretinoine in acne). The use of thalidomide derivatives with fewer side effects could be interesting but there is no data currently available relating to their potential neurotoxic effect. Given the unique nature and complexity of the mechanisms of action of thalidomide, which are not yet fully understood, new and unexpected indications could arise in the future, such as chronic heart failure or bleeding angiodysplasias, as recently reported[109-111].

Acknowledgements

The authors would like to thank J Bryant for reading the manuscript and for his helpful suggestions.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (**) to readers.


Excellent review discussing the immunomodulatory properties of thalidomide.


Recent data and extensive review of thalidomide’s pharmacokinetics.


Thalidomide: an old drug with new clinical applications


- An extensive review of the biological activity of thalidomide.


- This article provides an insight into the antiangiogenic properties of thalidomide.


- Good overview of the use of thalidomide in clinical oncology.


- An article on thalidomide analogues.


- A recent paper on thalidomide’s analogues using human data.
Recent data and extensive review of the use of thalidomide in multiple myeloma.


Thalidomide: an old drug with new clinical applications


• This article describes in detail the STEPS programme.


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Appendix 2

Thalidomide

E. LAFFITTE (1), J. REVUZ (2)

Le thalidomide est un médicament aux propriétés multiples, qui est utilisé essentiellement par les dermatologues du fait de son activité sur de nombreuses pathologies inflammatoires cutanées, mais qui est peu à peu redécouvert par d’autres spécialistes, en particulier les oncogénétologues.

**Propriétés biologiques [1]**

Le thalidomide possède différents modes d’action distincts et dont le mécanisme n’est pas toujours éclairci.

– Action hypnosédative : l’effet est différent des barbituriques, peut-être par une activation directe des centres du sommeil.

– Action immunomodulatrice : le thalidomide module l’équilibre entre les différentes classes de lymphocytes, mais il diminue surtout la synthèse du TNF-α par les monocytes humains stimulés en augmentant la dégradation de son ARN messager.

– Action anti-angiogène : cette propriété est médiée par l’inhibition de facteurs angiogènes dont le VEGF. Cette activité semble intéressante dans le traitement des néoplasies, pour lesquelles l’angiogenèse joue un rôle important.

**Pharmacologie [2]**

L’absorption orale est rapide, avec un pic plasmatique à 4 heures et une élimination par voie urinaire avec une demi-vie d’élimination plasmatique de 9 heures. Le thalidomide est retrouvé dans le sperme, avec une corrélation aux taux plasmatiques. Il n’existe pas de forme à usage parentéral, l’absorption cutanée est très basse et cette molécule n’est pas adaptée à un usage topique. Le thalidomide augmente l’action des barbituriques et de l’alcool, mais n’affecte pas le métabolisme des contraceptifs oraux.

**Indications en dermatologie**

Le thalidomide est employé dans des pathologies cutanées inflammatoires chroniques. Dans la majorité des cas, il n’a qu’une action suspensive ; les lésions récidivent à l’arrêt. Le thalidomide n’est pas contre-indiqué chez l’enfant où il est utilisé pour des indications similaires à celles de l’adulte.

**Indications clairement établies**

– Érythème noueux lépreux ou réaction lépreuse de type 2 ;

– aphthoses et ulcérations muqueuses sévères isolées ou associées à la maladie de Behçet (inefficace sur l’atteinte systémique) ou l’infection par le VIH ;

– infiltrat lymphocytaire cutané de Jessner et Kanoff ;

– lupus érythémateux cutané (inefficace sur l’atteinte systémique) ;

– GvH chronique à prédominance cutanée résistante aux immunosuppresseurs.

**Indications dermatologiques potentiellement intéressantes**

– Prurigos : nodulaire, actinique, du dialysé ;

– maladie de Kaposi ;

– érythème polymorphe chronique ou récidivant ;

– sarcoïdose cutanée ;

– pseudolymphomes.

**Autres indications plus anecdotiques**

– Histiocytose langerhansienne ;

– pyoderma gangrenosum ;

– pemphigoïde bulleuse et pemphigoïde cicatricielle ;

– pemphigus muqueux ;

– porphyrie cutanée tardive ;

– lichen plan, lichen érosif buccal ;
– maladie de Weber Christian ;
– syndrome de Melkersson-Rosenthal.

### Contre-indications

Pas de contre-indication absolue à part une grossesse évolutive ou désir de conception. Contre-indication relative en cas de neuropathie avérée (à part une neuropathie dans le cadre d’un érythème noueux lépreux (ENL), cf. tableau I) ou de pathologie thromboembolique évolutive.

### Effets secondaires (tableau II)

Certains effets secondaires du thalidomide sont majeurs, avec des conséquences graves, d’autres sont mineurs, apparaissant au début et disparaissant après diminution des doses.

### Effets secondaires majeurs

– Effet tératogène, pouvant théoriquement s’exprimer également chez la partenaire de l’homme traité, le thalidomide étant excrété dans le sperme ; il n’y a pas d’effet mutagène.

À noter que l’isotrétinoïne, prescrite de pratique courante dans l’acné chez des patientes en âge de procréer, est aussi tératogène que le thalidomide (risque de malformation fœtale de 25 à 30 p. 100 après une prise) ;

– neuropathie axonale, sensitive bilatérale et symétrique à début distal. Le risque semble maximal la première année de traitement, pour des doses supérieures à 25 mg/jour ;

– thromboses veineuses profondes ; pour des doses supérieures à 100 mg/jour, et chez des patients présentant des facteurs de risques thromboemboliques (syndrome des antiphospholipides, association avec des stéroïdes ou polychimiothérapie).

### Surdosage

La toxicité aiguë du thalidomide est très faible. Des surdosages accidentels ou volontaires n’ont eu aucune conséquence grave, même pour des doses de 14 g.

### Prescription et surveillance

La seule forme existante est la forme orale, sous forme de gélules dosées à 50 mg et 100 mg, distribuées en Europe par les laboratoires Pharmion.

### Modalités d’obtention

En France, le thalidomide ne peut être obtenue que par le biais d’un programme extrêmement strict de contrôle des prescriptions ayant pour but de prévenir toute grossesse sous

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**Tableau I.** – Indications clairement établies du thalidomide : posologies recommandées dans les indications dermatologiques habituelles.

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<tbody>
<tr>
<td>Érythème noueux lépreux (ENL)</td>
<td>100-400 mg/j en 2 prises jusqu’à sédation des signes, 7 jours en moyenne</td>
<td>diminution progressive jusqu’à 50 mg 2 fois par semaine</td>
<td>Pas de contre-indication en cas de neuropathie lépreuse dans le cadre d’un ENL : le thalidomide traite le processus inflammatoire périphérique et améliore les symptômes neurologiques</td>
</tr>
<tr>
<td>Aphtoses et ulcérations muqueuses sévères (dont VIH et Behçet)</td>
<td>100-200 mg/j pendant 1 mois</td>
<td>diminution progressive jusqu’à 50 mg 2 fois par semaine</td>
<td>Après échec de la colchicine</td>
</tr>
<tr>
<td>Lupus cutané</td>
<td>100-200 mg/j pendant 1 mois</td>
<td>50 mg/j à 50 mg 2 fois par semaine</td>
<td>En deuxième intention si contre-indication ou inefficacité de 3 mois d’antipaludéens de synthèse</td>
</tr>
<tr>
<td>Infiltrat lymphocytaire cutané de Jessner-Kanoff</td>
<td>100-200 mg/j pendant 1 mois</td>
<td>50 mg/j à 50 mg 2 fois par semaine</td>
<td>Efficacité purement suspensive, une récidive survenant 2 à 3 semaines après l’arrêt du traitement</td>
</tr>
<tr>
<td>Réaction du greffon contre l’hôte (GvH) après greffe de moelle allogénique</td>
<td>600-800 mg/j chez l’adulte 12 mg/kg/j chez l’enfant</td>
<td></td>
<td>Dans les formes chroniques à prédominance cutané résistantes aux traitements immunosuppresseurs, Pas d’effet dans la prévention de la GvH chronique ou dans la GvH aiguë</td>
</tr>
</tbody>
</table>
Thalidomide

Tableau II. – Effets secondaires du thalidomide [2, 3].

<table>
<thead>
<tr>
<th>Effets secondaires du thalidomide</th>
<th>FRÉQUENTS</th>
<th>MOINS FRÉQUENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Majeurs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Tératogénicité</td>
<td></td>
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<tr>
<td>Neuropathie périphérique</td>
<td></td>
<td></td>
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<tr>
<td>Thromboses veineuses profondes</td>
<td></td>
<td></td>
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<tr>
<td><strong>Mineurs (mais peuvent être limitant à haute dose)</strong></td>
<td></td>
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<tr>
<td>Somnolence</td>
<td></td>
<td></td>
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<tr>
<td>Constipation, prise de poids, douleurs abdominales</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cutanés</strong></td>
<td></td>
<td></td>
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<tr>
<td>Eruption cutanée maculopapuleuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Érythème polymorphe, syndrome de Lyell, érythrodermie, érythème noueux</td>
<td></td>
<td></td>
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<tr>
<td>Vasculite</td>
<td></td>
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<tr>
<td>Fragilité ungulaire</td>
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<tr>
<td>Sécheresse buccale</td>
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<tr>
<td>Prurit</td>
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<tr>
<td>Érythème palmoplantaire</td>
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<tr>
<td><strong>Endocriniens</strong></td>
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<tr>
<td>Hypothyroïdie</td>
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<tr>
<td>Aménorrhée</td>
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<tr>
<td>Galactorrhée</td>
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<tr>
<td>Saignements génitaux</td>
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<tr>
<td>Hypoglycémie/hyperglycémie</td>
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<td><strong>Hématologiques</strong></td>
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<tr>
<td>Leucopénie</td>
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<tr>
<td><strong>Neuropsychiquestes</strong></td>
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<tr>
<td>Maux de tête</td>
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<td></td>
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<tr>
<td>Tremblements intermittents</td>
<td></td>
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<tr>
<td>Démence réversible</td>
<td></td>
<td></td>
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<tr>
<td>Dépression</td>
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<tr>
<td>Perte de libido</td>
<td></td>
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<tr>
<td><strong>Gastro-intestinaux</strong></td>
<td></td>
<td></td>
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<tr>
<td>Distension abdominale</td>
<td></td>
<td></td>
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<tr>
<td>Augmentation de l’appétit</td>
<td></td>
<td></td>
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<tr>
<td>Nausées</td>
<td></td>
<td></td>
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<tr>
<td>Hépatite</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Système cardiovasculaire</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardie, tachycardie</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension, hypotension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thalidomide est une molécule puissante qui représente une option thérapeutique très utile dans de nombreuses pathologies dermatologiques difficiles à traiter. Les principaux effets secondaires peuvent être minimisés avec une bonne sélection des patients, en particulier en identifiant les facteurs de risques de neuropathie et d’accidents thromboemboliques. Les médecins prescripteurs ne doivent donc pas être effrayés par le thalidomide, qui reste une molécule utile pour de nombreuses pathologies, sous réserve d’une surveillance rigoureuse.

Conduite du traitement et surveillance

– Posologies : cf. tableau I ;

Thalidomide sur Internet

Plusieurs sites traitant du thalidomide sont actuellement consultables sur Internet :

Conclusion

FICHE PRATIQUE – THALIDOMIDE

Avant le traitement

Formalités administratives

Avec la pharmacie hospitalière : déclaration en ATU de cohorte ou nominative en fonction de l’indication
Avec l’Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS, service des ATU) : un accord préalable doit être obtenu en cas d’ATU nominative
Avec le patient : information concernant les risques tératogènes et signature d’un accord de soins et de contraception

Bilan pré-thérapeutique

Examen neurologique et EMG
TSH
Chez la femme en âge de procréer : dosage de βHCG qui doit être négatif 3 jours avant le début de la prescription

Mise en place d’une contraception par 2 méthodes efficaces (femme), port du préservatif (homme)

Pendant le traitement

Administration
Prise recommandées le soir (somnolence)
Ordonnance mensuelle de renouvellement

Surveillance

Mensuelle : examen neurologique, dosage de βHCG chez la femme en âge de procréer
Semestrielle : EMG
Contre-indication : grossesse, dons de sang et de sperme

Après le traitement

Grossesse possible
– Chez la femme : dès le premier cycle suivant l’arrêt du traitement
– Chez l’homme : attendre 3 mois après arrêt du traitement (correspondant à un cycle de spermatogenèse)
Appendix 3

Thalidomide, well known by dermatologists for its anti-tumor necrosis factor-α activity, is used for several inflammatory cutaneous disorders. Anti-angiogenic properties of thalidomide, mediated by inhibition of angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor, were first shown in 1994 on a rabbit cornea model [1]. Since the mid 1990’s, the discovery of this anti-angiogenic effect has led to renewed interest for this drug, especially in oncology [2]. Thalidomide has been shown to be an active and promising anti-carcinogenic drug, as a single agent or in combination with dexamethasone in hematological malignancy, such as relapsing or refractory multiple myeloma, myelodysplasia or acute myeloid leukemia [3]. Since Kaposi sarcoma (KS) is an angiogenic neoplasm, it has been logically hypothesized that thalidomide might be of interest in KS.

Thalidomide was first studied in HIV-associated KS. In four publications that involved a total of 50 patients [4–7], well reviewed and analyzed by Krown [8], 17 patients (34%) showed objective KS regression. Dosages ranged from 100 to 1,000 mg/day during 8 weeks to 12 months; no complete response was observed, and HHV-8 viral load was reduced only in 3 responding cases. Eleven patients (22%) withdrew because of toxicity.

In this issue of Dermatology, the effect of thalidomide is assessed for non-HIV KS (iatrogenic or classic) in two retrospective studies [9, 10]. In the first study, Rubegni et al. [9] treated 3 patients with 100 mg/day of thalidomide for 1 year and observed a complete response in 2 patients (including an immunosuppressed patient with systemic KS) and a partial response in the third. In the two responding cases, they observed a normalization of the HHV-8 viral load in the skin and the blood. In the second study [10], 11 patients were treated with a median dose of 100 mg/day for a median time of 3 months. The results are less impressive, with only 3 patients (27%) achieving a partial response. Out of these 14 patients, 4 (28%) discontinued thalidomide for side-effects. The overall response rate appears thus to be quite similar in KS, whether HIV associated or not, and lower than the response rates obtained with other systemic therapies such as interferon, pegylated liposomal doxorubicin [10] or even radiotherapy in localized cases [11].

Taken together, these results suggest that thalidomide is not a major therapy for KS, with a disappointing response rate and limitations due to side-effects, although it could be useful in some specific cases as shown by Rubegni et al. [9]. However, an anti-angiogenic approach may still be interesting in KS, as suggested by Ben M’barek et al. [10]. With the ‘rediscovery’ of thalidomide, several structural analogues have been developed in an attempt to find compounds with thalidomide’s properties without the associated side-effects. In particular, lenalido-
mide (Revlimid®), a second-generation thalidomide derivative, has been extensively studied in patients with myelodysplastic syndromes. Lenalidomide was identified as more potent than thalidomide and devoid of many of the serious adverse reactions associated with thalidomide administration, such as neuropathy [12]. Moreover, it has been recently shown that oral administration of lenalidomide inhibits angiogenesis in rat in vivo models [13]. Thus, lenalidomide could be the next promising step for an oral anti-angiogenic therapy in KS.

References

Appendix 4

Thalidomide, semen distribution, teratogenicity... and cost

DOI: 10.1111/j.1365-2133.2005.07083.x

Sm, I read with interest the recent article on thalidomide in this journal by Wu et al.1 with the detailed recommendations to prevent thalidomide embryopathy. However, I have two remarks.

First, the authors do not mention that there is a potential risk of a teratogenic effect of thalidomide with treated male patients, as the molecule is distributed into semen. In rabbits, the molecule is not only present in the seminal fluid, but is also firmly fixed on spermatozoa.2 In humans, after an oral intake of 100 mg daily, thalidomide is detected in semen at week 4 with a correlation between plasma and semen levels.3 Congenital malformations have been observed in newborn rabbits resulting from breeding experiments with males having a prolonged intake of thalidomide.4 Such an effect has not yet been described in humans, but there could be a potential risk of fetal exposure to thalidomide in pregnant women through transmission by semen of treated male patients.5 As a consequence, men treated with thalidomide should avoid sperm donation, and use condoms during the therapy and for 3 months after its cessation (corresponding to a spermatogenesis cycle).

Secondly, one should notice that some other highly teratogenic molecules are frequently prescribed by dermatologists, such as isotretinoin. It has been demonstrated that approximately 25–30% of fetuses exposed to isotretinoin have birth defects,6 which makes isotretinoin as embryotoxic as thalidomide. There are some specific birth control programmes associated with isotretinoin use, such as the SMART (System to Manage Accutane-Related Teratogenicity) programme in the U.S.A.,7 which are not as comprehensive or expensive as the STEPS (System for Thalidomide Education and Prescribing Safety) programme. However, the Food and Drug Administration has recently approved a strengthened risk management programme for isotretinoin called iPLEDGE, use of which will become mandatory in the U.S.A. on 31 December 2005.7

Thus, dermatologists should not be afraid of thalidomide, as teratogenicity is currently well controlled in Western countries through managed effective contraceptive methods and repeated pregnancy tests. This is not true everywhere in the world, and at least 34 cases of embryopathy after exposure to thalidomide have been reported in South American leprosy endemic areas since 1965.8

The main factors limiting the use of thalidomide are currently its neurotoxicity, and the weightiness of the STEPS programme (and its equivalent in Europe, the Pharmion Risk Management Programme, PRMP) which is time consuming and requires laborious inputs from prescriber, patient and pharmacist. Another limiting factor is the price of the drug, which has increased 400% since the sponsorship was transferred to Pharmion Development in Europe, with the introduction of the PRMP. Health insurances often do not pay for this orphan drug, and therefore patients may have to bear much of the cost themselves. This fact should also have been discussed by Wu et al.

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E-mail: emmanuel.laffitte@chuv.ch

References


3 Teo SK, Harden JL, Burke AB et al. Thalidomide is distributed into human semen after oral dosing. Drug Metab Dispos 2001; 29:1355–7.


Appendix 5

Estimation of cost-of-illness in patients with psoriasis in Switzerland

Alexander A. Navarin, Emanuel Laffitte, Curdin Conrad, Paolo Piffaretti, Elisabeth Brock, Stephan Ruckdaeschel and Ralph M. Trüeb

Introduction

Psoriasis is a chronic inflammatory skin disease with a substantial economic burden [1-9]. It is highly prevalent, affecting about 2% of the adult Western population. The chronic, very noticeable and symptomatic skin lesions frequently result in work day loss. Discomfort, time and energy invested in treatment and the stigmatization associated with the disease have significant adverse impact on quality-of-life. Due to lack of a definite cure, continuous care is often required.

As psoriasis is not a life-threatening disease, the medical and socioeconomic burden are often underestimated by health care professionals. However, for several Western countries, it has been shown that psoriasis represents a financial burden both for the affected individual and for the health care system [1-9]. According to reports from Germany [7-9], cost estimates range from about €160 million [10] for inpatient treatment per year to annual severity-related costs of €2'866 per patient per year for moderate psoriasis to €4'985 for severe psoriasis in one study [7], and mean total costs of €6'709 per patient per year in the other study [8]. In contrast, little is known about the economic impact of psoriasis in Switzerland, specifically, there is a lack of knowledge regarding out-of-pocket expenses and ambulatory care costs. However, both of these expenditures play an important budgetary role for psoriasis patients and their families. Thus, the present study was initiated in order to estimate the impact of psoriasis in terms of resources used, associated costs, and quality of life impairment, specifically for Switzerland. This is intended to convey a picture of the burden of the disease, which can be used in evaluations of the cost-effectiveness of specific therapies, i.e. new therapeutic agents for effective psoriasis control.

Design and Methods

Hypothesis

1. Patients with plaque-type psoriasis in Swiss dermatological practices and outpatient clinics as well as patient members of the Swiss Psoriasis and Vitiligo Association show a substantial and disease-activity dependent burden of illness.

2. Direct costs of the disease rise disproportionally with disease activity.

Design of the study

The study is a retrospective cost-of-illness analysis in relation to severity of disease. It is based on data collected through a patient survey to evaluate the impact of disease on health-related quality of Life (HRQoL) and patients’ out-of-pocket expenses, a physicians’ survey to estimate ambulatory care costs, and inpatient data obtained from the Federal Statistical Office (FSO) regarding the number of cases treated for psoriasis in the hospital and average length of hospital stay. Patients covered by the two surveys were not identical. The reference year for data collection for outpatients was 2005, for inpatients 2004.
The objective of the study was to obtain data on out-of-pocket expenses, costs of outpatient/office-based care and inpatient care for psoriasis, and to extrapolate total costs by state of severity in the entire Swiss population.

**Aim of the study**

The burden of disease for the individual patient in terms of health-related quality of life and the disease’s impact on daily activities was measured with the Dermatology Life Quality Index (DLQI) [11].

Collected data were assessed for plausibility and completeness by two experienced representatives of HealthEcon. Incompletely filled questionnaires were conservatively completed if necessary by applying information from patients that provided valid reports for the respective category or item of resource use. Where no plausible data regarding i.e. treatment costs could be identified based on other patients in the same survey, data was substituted based on official publications such as the Drug Reference Manual of Switzerland (“Arzneimittel-Kompendium der Schweiz”) or other sources. Missing data was supplemented in such a way as to underestimate costs, rather than overestimating them.

**Data Collection – Physicians**

Similar to the patient survey, data on resource use in ambulatory care were collected using a “bottom-up” approach based on a specifically developed semi-structured, self-reported questionnaire for physicians. The physician questionnaire requested information on demographics, assessment of disease severity (using the Psoriasis Area Severity Index (PASI) if available), co-morbidities, drugs, medical services and rehabilitation.

The information concerning resource consumption was retrospectively extracted from the patient’s records. The documentation of drug treatment was structured according to different drug classes. Based on prescription information the overall costs of drugs were calculated by multiplying the prescriptions with the corresponding prices. Regarding medical services, the participating dermatologists were asked to document the frequency of diagnostic and therapeutic procedures performed for the given patient, including a wide range of services from basic consultation to, e.g. phototherapy. Given this structural framework, the questionnaire demanded the documentation of the medical and technical services provided, the number of applications, the respective Tarmed (individual outpatient service tariff) position and/or tax points. The costs of this service charged to the Swiss obligatory health insurance were calculated by multiplying frequency, tax points and tax point value. Missing data were, if necessary, conservatively supplemented in such a way as to underestimate costs, rather than overestimating them.

**Data Collection – FSO, SVK**

Extracting costs for inpatient care differs from the data obtained through the patient and physician survey in that it used a “top-down” approach instead of the “bottom-up” calculation used to estimate costs for ambulatory care and out-of-pocket expenses. The information supplied by the FSO regarding the number of cases treated in the hospital for psoriasis and the average length of stay (LOS) was translated into number of patients by using the rate “cases per patient” also supplied by the FSO. Average LOS per patient in 2004 was calculated on the number of cases per ICS-10 subgroup, the average length of stay per case, and the number of cases per patient. As all patients hospitalized with the respective diagnosis are included, the data provides a total sum of costs for inpatient care caused by patients hospitalized due to psoriasis. Costs of inpatient care calculated that way are the total costs...
incurred for Switzerland that year. Along common Swiss medical practice, as a rule only severe psoriasis cases require hospital treatment. The costs for inpatient care as derived from FSO data were therefore completely assigned to patients with severe psoriasis when extrapolating the costs of psoriasis for Switzerland. In 2005, 229 patients received biologic treatment for severe psoriasis. The respective costs were obtained from the “Schweizerischer Krankenkassen Verband” (SVK, Swiss Medical Insurance Association).

Costs

Patients estimated their resource use regarding OTC medication, skin care products, as well as non-reimbursed treatments. The overall costs estimate for each of the surveyed patients was calculated by multiplying the amount of units of psoriasis-related physical resources consumed by each patient with the costs per unit given by the patient or – depending on the patient’s reporting – by adding up the total amount of expenses the patient reported to have spent for products or services in 2005. This calculation was performed differentiating for disease severity (mild, moderate, severe) and resulted in total costs for patients in the respective category of severity.

To evaluate ambulatory treatment costs as reported by physicians, the average frequency of diagnostic or treatment services was multiplied with the corresponding cost for this service. Charges for outpatient services were estimated using points published in the Swiss tariff list (Tarmed) multiplied by the average value per point based on the straight unweighted arithmetic mean of the tax point values across all cantons of Switzerland for 2005, which was CHF 0.86 (for procedures and services). For laboratory tests, a national rate of CHF 1.00 per tax point was applied. Tarmed positions and associated tax points were obtained from the Tarmed Browser 1.2 which was valid for the year 2005. The 2005 tax point values were obtained from Santesuisse’s website (www.santesuisse.ch/datasheets/files/200602011439030.xls) in June 2006. Respective data for laboratory tests were obtained in June 2006 from the document “Analysenliste” on the website of the Swiss Ministry of Health (www.bag.admin.ch/kv/gesetze/d/index.htm). Drug prices were obtained from the 2005 Drug Reference Manual of Switzerland. Like for the patient survey, costs calculated in this way were added up over all patients who were reported being given a specific drug or service in 2005 to result in total costs for all patients that reported use of this particular parameter in the respective category of disease severity (mild, moderate, severe).

To estimate the costs of inpatient care a targeted analysis of Swiss Hospital Statistics was used. Costs for inpatient care was estimated by multiplying the average LOS per patient with the average costs per hospital day. In 2005 the average costs per day in hospital amounted to approximately CHF 1’070 [12].

Results

Patient survey

383 documented records of patients’ out-of-pocket expenses were returned (32%, comparable to other questionnaire-based studies [13]) and analyzed. The majority of patients were between 30 and 65 years old, with the mean at 55 years. 226 (59%) of the 383 patients were male. In 50% of patients, psoriasis had been diagnosed between 55 and 25 years ago and in 41% between 5 and 25 years ago. In 60% of cases, the diagnosis had been posed by a dermatologist.

Using the body surface area affected as a measure for severity, 38% reported mild disease (BSA <2%), 43% moderate disease (BSA 2-10%) and 19% severe disease (BSA > 10%). On average, patients reported more than seven affected body areas. The relative proportion of body areas affected is shown in Table 1.

Overall 65% of patients had been using drugs against psoriasis one month prior to filling out the questionnaire. 8% reported having been free of symptoms during the previous week. Out-of-pocket expenses relating to the category of severity are shown in Table 1. We found a considerable increase in total average out-of-pocket expenses depending on the severity of disease from CHF 630 per patient and year in mild psoriasis to CHF 2’400 in severe psoriasis. 30% of patients reported a large or very large effect of their psoriasis on quality of life, two thirds indicated a small or moderate influence, and only 8% reported no effect. The greater the affected skin area, the higher the impact on the quality of life (Figure 1).

Physician survey

170 patients were documented by 57 dermatologists. Comparable to the patient survey, the majority of patient was between 30 and 65 years old, with a mean age of 48 years. 19% of patients were diagnosed with psoriasis between 55 and 25 years ago, 58% between 25 and 5 years ago, and 18% less than 5 years ago.

Disease activity of psoriasis documented by the dermatologists was skewed towards higher severity compared to the patient survey: 34% were reported as severe and 22% as moderate. In 21 patients, PASI scores had been measured with the mean at 12.5. Patients indicated more involvement of nail (54% vs. 31% by dermatologists), scalp (82 vs. 68% by dermatologists), and intertriginous (arm pits, genital, anal region) regions (19 vs. 9%, 32 vs. 25%, 33 vs. 20% resp. by dermatologists) than identified by the dermatologists.

The results of the physician survey show the same trend of costs rising disproportionately with disease severity: ambulatory costs range on average from CHF 1’100 per patient per year for mild psoriasis, to CHF 2’500 for moderate psoriasis and CHF 9’900 for severe psoriasis. As expected, a relation between ambulatory costs and severity of disease was observed (Table 3).
In 2005, some patients with severe psoriasis received biologics, namely Enbrel (Etanercept), Amevive (Alefacept) or Raptiva (Efalizumab), resulting in total costs of CHF 2'154'547. These costs were added to the treatment cost for severe psoriasis.

**Inpatient care**

Based on ICD-10 codes a total of 3'578 cases referring to 3'043 patients with diagnosis of psoriasis were registered in Swiss hospitals in 2004. An average LOS of 16.71 days per hospitalized male patient and 20.68 days per hospitalized female patient was reported, resulting in a weighted average LOS for men (60%) and women (40%) of 18.3 days.

Resource use is documented by the Swiss hospital statistics in terms of the average length of stay (LOS) in days per case. The reported 3'578 cases corresponded to 3'043 patients in 2004. Based on a weighted average LOS of 18.3 days and average costs for one hospital day of approximately CHF 1’070 [12], the costs of inpatient care amounts to approximately CHF 17’800 per year for a male and CHF 22’100 per year for a female patient hospitalized for psoriasis.

**Extrapolating total direct costs of moderate-to-severe psoriasis for Switzerland**

Total costs of psoriasis for Switzerland were estimated for an estimated adult population of 5.8 million based on the numbers reported by the SFO. Assuming a conservative overall prevalence rate of psoriasis of 1.5% based on observed prevalence rates in Western countries of 2-3% [2, 3, 14-17], a psoriasis patient population was of 86’170 was assumed in Switzerland.

To extrapolate costs, we used both the relative distribution of the categories of psoriasis severity gained from the patient survey, namely 38% mild, 43% moderate and 19% severe psoriasis (Table 4, left half), as well as the often cited distribution by Crown et al. [18], with 79% of patients indicating mild, 12% moderate and 9% severe psoriasis (Table 4, right half).

Costs per patient increase considerably with the degree of disease severity, i.e. total costs per patient per year double from CHF 1’800 in mild psoriasis to CHF 3’600 in moderate psoriasis and increase exponentially to between CHF 17’000-20’000 in severe psoriasis. Costs per severe patient vary with changes in prevalence rate as the costs of inpatient care were exclusively assigned to severe psoriasis as described above.

The total direct cost of psoriasis in Switzerland is approximately CHF 314 to 458 million per year (cost basis year 2005), depending on the severity distribution pattern used for the analysis and considering out-of-pocket-expenses as well as costs for ambulatory and inpatient care (Table 4).

**Discussion**

The aim of this study was to estimate the cost-of-illness for patients with psoriasis in Switzerland from both a societal and individual perspective. In addition to the socioeconomic impact of psoriasis for the whole society, the disease imposes a high financial burden on the patients themselves. To obtain data on out-of-pocket expenses and costs of outpatient/office-based care, surveys were distributed to members of the Swiss Psoriasis and Vitiligo Society (SPVG), and office–hospital-based Swiss dermatologists, respectively. Additional inpatient costs were calculated on the basis of data obtained from the Federal Statistical Office (FSO) regarding the number of cases treated for psoriasis in the hospital and average length of hospital stay.

Cost-of-illness studies are a well-recognized tool to show the financial burden of diseases in a particular country and to identify subgroups for which the costs are particularly high. Regardless of the specific health system, cost-of-illness studies on psoriasis so far performed indicate considerable economic consequences in countries such as the UK [1], Italy [3], the USA [4], Australia [5], and Germany [7-9]. These studies have shown that the costs for psoriasis patients depend on disease severity, with higher costs in the more severe cases. For this reason the resulting empirically derived cost estimates for psoriasis extrapolated to the total adult population of Switzerland was of particular interest for patients with moderate-to-severe psoriasis. One of the distinguishing characteristics of this study is that it is the first to present total psoriasis-related costs on a patient-covered out-of-pocket basis and in an outpatient setting.

In the US the 1998 National Psoriasis Foundation patient-membership survey identified 40% of the psoriasis patients to suffer from severe psoriasis (Krueger, Arch Dermatol 2001; 137: 280-4), resulting in a prevalence of severe psoriasis of 0.8% in the general population. However in a population-based study the prevalence of severe psoriasis was found to be ten times less (0.06% of the general population) (Stern, J Invest Dermatol Symp Proc 2004; 9:136-9). Our calculation results were in the range between these two publications, with a prevalence of 0.77% for moderate to severe psoriasis. The proportion of patients with mild (37%), moderate (42%) or severe psoriasis (19%) found here differs somewhat from the epidemiological figures of often cited other works that have identified 21% of all patients to suffer moderate to severe psoriasis [19], of which 56% have moderate and 44% severe psoriasis [7]. Based on these figures, an estimated 79% of patients would have mild, 12% moderate and 9% severe psoriasis. Our distribution might therefore not be representative for the general population. Our sample was composed out of patient members of the SPVG and patients treated in dermatologic practices. Both groups might be skewed towards higher severity of psoriasis. In addition, the patients’ own estimation of body surface might be incorrect, however we believe this to be unlikely, because relative accuracy of patients’ estimations with a much more complicated
instrument (SAPASI) has been described [20]. To obtain a sound estimate of costs, we used both severity pattern distributions (Table 4) for the calculations, reaching comparable total cost within a range of 31% (CHF 314 – 458 million).

We found a relationship between the patient-reported effect of psoriasis on quality of life and the severity of disease as represented by the body surface area affected. The finding is not unexpected, as it corresponds to a recently published report [9].

Potential limitations of this study include the rather low response rate of 32%. It is possible that the patients with higher quality of life impairment responded to a larger extent than patients with comparable to the literature [13, 21, 22], and a possible recall bias of patients regarding their out-of-pocket expenses over the past 12 months. In addition, personal expenses on certain products, such as skin care products and dietary supplements, do not necessarily reflect the patient’s current disease status, but may merely reflect habitual use. As this study included only patients that are in the SPVG or receiving treatment by a dermatologist, both with presumably relatively high loss of quality of life, the proportion of patients that treat their psoriasis minimally was not included. In addition, patients organized in patients groups are likely to spend more money on their illness. The issue of missing data and the need to make some assumptions is of general concern in any questionnaire-based survey. This was addressed by attempting to make assumptions likely to lead to an underestimate of costs, rather than an overestimate, i.e. such as assuming the use of the smallest package size if information on package size was missing. Regarding the cost of hospitalized patients, we could not differentiate whether all patients were in the hospital for their psoriasis or had psoriasis as a secondary diagnosis. Therefore, the real cost generated for the treatment of psoriasis in the hospital setting might be somewhat lower.

Despite these limitations, the estimate provided by this study offers an approximation of the direct costs associated with psoriasis in Switzerland. The results obtained were comparable to the results from former studies in other countries [6-8]. In Germany, costs for inpatient treatment are estimated at approximately € 160 million (CHF 239 million) [10] per year, compared to € 39 million (CHF 59 million) in Switzerland. This result is in line with the difference in population and higher Swiss hospital costs. Regarding annual severity-related costs, one German study reported costs of € 2'866 (CHF 4'281) per patient and year for moderate, and € 4'985 (CHF 7'447) for severe psoriasis [7]. Another study estimated mean total costs as € 6'709 (CHF 10'000) per patient and year [8]. The corresponding costs in Switzerland amount to approximately € 2'410 (CHF 3'600) per patient per year for moderate to approximately € 12'000 (CHF 16'000-20'000) for severe psoriasis.

The results of the present study indicate that the total burden of psoriasis in Switzerland amounts to approximately CHF 312-458 million per year (cost basis year 2005). This represents between 0.6-1.1% of total direct health care expenditures in 2005 in Switzerland. Although the estimated total direct costs for psoriasis amount to approximately 1% of total health care expenditures in Switzerland, these costs are incurred by a relatively small group of patients (1-2% of total population).

In conclusion, the present study indicates that psoriasis imposes a substantial economic burden on Swiss society, the health insurance system, and the affected individuals themselves. The Swiss health insurance system is confronted with high direct in- and outpatient treatment costs of CHF 312-458 million per year. Moderate-to-severe psoriasis is associated with significant impact on quality of life and important costs, indicating need for efficient control of the disease. This cost-of-illness study provides specific health economic data for further healthcare decision making, particularly with the advent of new therapeutic agents that require economic assessment.

Acknowledgements and Disclosure of Interest

The study was carried out by HealthEcon Ltd., Basel and funded by Wyeth Pharmaceuticals Ltd., Zug, Switzerland. Particularly we would like to thank the participating patients and their organization, the Swiss Psoriasis and Vitiligo Society (SPVG), as well as contributing 57 Swiss dermatologists for their cooperation in the surveys. The design, analysis and reporting of the study was performed by HealthEcon Ltd. according to pre-set objectives unrestricted by Wyeth Pharmaceuticals Ltd. and with the scientific advice of RMT. Paolo Piffaretti is a representative of Wyeth. Elisabeth Brock and Stephan Ruckdaeschel are employed by HealthEcon Ltd.
Table 1: Body areas affected as reported from patient and physician survey (multiple answers were possible)

<table>
<thead>
<tr>
<th>Body area affected</th>
<th>Results from patient survey</th>
<th>Results from physician survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number and proportion of patients reporting respective area (n=383)</td>
<td>Number and proportion of dermatologists reporting respective area (n=170)</td>
</tr>
<tr>
<td>Back</td>
<td>193 (50.40%)</td>
<td>109 (64.10%)</td>
</tr>
<tr>
<td>Feet</td>
<td>136 (35.50%)</td>
<td>60 (35.30%)</td>
</tr>
<tr>
<td>Knee</td>
<td>244 (63.70%)</td>
<td>112 (65.90%)</td>
</tr>
<tr>
<td>Nails</td>
<td>208 (54.30%)</td>
<td>60 (35.30%)</td>
</tr>
<tr>
<td>Arms</td>
<td>72 (18.80%)</td>
<td>16 (9.40%)</td>
</tr>
<tr>
<td>Elbows</td>
<td>221 (57.70%)</td>
<td>111 (65.30%)</td>
</tr>
<tr>
<td>Genitals</td>
<td>124 (32.40%)</td>
<td>43 (25.30%)</td>
</tr>
<tr>
<td>Legs</td>
<td>275 (71.80%)</td>
<td>124 (72.90%)</td>
</tr>
<tr>
<td>Scalp</td>
<td>314 (80.00%)</td>
<td>116 (68.20%)</td>
</tr>
<tr>
<td>Face</td>
<td>130 (33.90%)</td>
<td>40 (23.50%)</td>
</tr>
<tr>
<td>Hands</td>
<td>160 (41.80%)</td>
<td>73 (42.90%)</td>
</tr>
<tr>
<td>Sacral bone</td>
<td>135 (35.20%)</td>
<td>66 (38.80%)</td>
</tr>
<tr>
<td>Upper part of body</td>
<td>167 (43.60%)</td>
<td>103 (60.60%)</td>
</tr>
<tr>
<td>Anal region</td>
<td>128 (30.40%)</td>
<td>34 (20.00%)</td>
</tr>
</tbody>
</table>

Table 2: Out-of-pocket expenses per patient per year according to state of severity

<table>
<thead>
<tr>
<th>State of Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Category</td>
<td>Mean Costs [CHF]</td>
<td>Valid N</td>
<td>Mean Costs [CHF]</td>
</tr>
<tr>
<td>Prescribed Drugs</td>
<td>720 (n=38)</td>
<td>1679 (n=74)</td>
<td>8466 (n=58)</td>
</tr>
<tr>
<td>Medical Services</td>
<td>416 (n=38)</td>
<td>813 (n=74)</td>
<td>1413 (n=58)</td>
</tr>
<tr>
<td>Total Ambulatory Care</td>
<td>1136 (n=38)</td>
<td>3222 (n=74)</td>
<td>9978 (n=58)</td>
</tr>
</tbody>
</table>

Table 3: Costs of ambulatory care per patient per year according to state of severity

<table>
<thead>
<tr>
<th>State of Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Category</td>
<td>Mean Costs [CHF]</td>
<td>Valid N</td>
<td>Mean Costs [CHF]</td>
</tr>
<tr>
<td>Drugs</td>
<td>1’387’674</td>
<td>1’820’325</td>
<td>5’518’079</td>
</tr>
<tr>
<td>Skin Care Products</td>
<td>4’377’296</td>
<td>7’367’522</td>
<td>5’315’580</td>
</tr>
<tr>
<td>Bathing Therapy</td>
<td>841’092</td>
<td>202’362’599</td>
<td>1’483’881</td>
</tr>
<tr>
<td>Other Measures</td>
<td>6’965’743</td>
<td>11’270’946</td>
<td>15’130’220</td>
</tr>
<tr>
<td>Total out-of-pocket expenses</td>
<td>20’534’544</td>
<td>41’429’982</td>
<td>40’960’701</td>
</tr>
<tr>
<td>Prescribed Drugs</td>
<td>25’424’898</td>
<td>61’989’812</td>
<td>143’585’475</td>
</tr>
<tr>
<td>Medical Services</td>
<td>12’534’424</td>
<td>30’101’815</td>
<td>23’599’655</td>
</tr>
<tr>
<td>Total costs for ambulatory care</td>
<td>36’969’321</td>
<td>92’011’626</td>
<td>98’758’362</td>
</tr>
</tbody>
</table>

Table 4: Total Costs across all Categories of Severity in Switzerland

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated prevalence rate 1.5%, costs calculated with commonly assumed severity grades:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Drugs</td>
<td>53’984’983</td>
</tr>
<tr>
<td>Skin Care Products</td>
<td>133’441’608</td>
</tr>
<tr>
<td>Bathing Therapy</td>
<td>267’727’942</td>
</tr>
<tr>
<td>Other Measures</td>
<td>586’178’951</td>
</tr>
<tr>
<td>Total costs of moderate to severe psoriasis</td>
<td>401’014’470</td>
</tr>
<tr>
<td>Total costs across all states of severity</td>
<td>579’301’966</td>
</tr>
<tr>
<td>Total costs per patient and severity</td>
<td>1’708</td>
</tr>
</tbody>
</table>

"Valid N" denotes the number of patients reporting valid data for any particular cost category. 16 patients with severe psoriasis reported out-of-pocket expenses for drugs in 2005. Dividing the total expenses on drugs reported by these 16 patients (in total approximately CHF 23’000; not shown in this table) by all patients with severe psoriasis (n=71) results in the average out-of-pocket expenses of CHF 330 for drugs per patient in the severe state of disease. Without this change in denominator the respective expenses would be overestimated.
Figure 1: Relation between Disease Severity and Impact on Quality of Life

References
Appendix 6

 INTRODUCTION
Le psoriasis unguéal est fréquent, interåre sévèrement avec la qualité de vie des patients (1), et est de traitement difficile, surtout lorsque l'atteinte est multiple. Nous rapportons l'efficacité des anti TNFα (infliximab et etanercept) dans un cas de psoriasis cutané et unguéal.

OBSERVATION
Un homme de 45 ans, était hospitalisé pour une poussée de psoriasis cutané étendu avec atteinte des 20 ongles, sans amélioration après deux mois de traitement par 25 mg/semaine de méthotrexate (MTX). Des injections intraveineuses d'infliximab (Rémicade®) étaient ajoutées. Le patient était blanchi en 21 jours. Après 4 mois de traitement, les ongles des mains étaient redevenus normaux.

Après 10 mois, le MTX et l'infliximab étaient interrompus suite à un abcès périanal, les lésions cutanées et unguéales récidivaient. La reprise du MTX associé à des injections sous cutanées d'etanercept (Enbrel®) contrôlait le psoriasis cutané et unguéal en 4 mois.

COMMENTAIRES
La prise en charge du psoriasis unguéal avec atteinte multiple est difficile. Les traitements locaux sont inadaptés, les traitement systémiques peuvent être efficaces, souvent en parallèle avec l'atteinte cutanée (1). Les traitements biologiques dirigés contre le TNFα semblent améliorer le psoriasis unguéal, mais leur action ne pourrait être que suspensive, comme pour les autres traitements du psoriasis.

REFERENCES
Appendix 7

INTRODUCTION

The therapy of severe psoriasis is difficult in patients with chronic hepatitis C. We report two cases of psoriasis in patients with chronic, active hepatitis C, treated with etanercept without worsening of the hepatitis.

CASES REPORT

Two patients were followed for chronic active hepatitis C and a severe psoriasis. A treatment with etanercept, 25 mgx2 per week was started. The psoriasis was improved (obtaining the PASI 90 for a case, and PASI 75 for the other), the viremia and hepatic parameters remained stable with respectively 16 and 9 months of follow-up.

The association chronic active C hepatitis and psoriasis is a real therapeutic challenge. The hepatitis contra-indicates the use of methotrexate or ciclosporine, the psoriasis may be worsen by interferon and ribavirin. In our two cases, the psoriasis was controlled and the hepatitis remain stable.

Almost thirty cases of inflammatory rheumatic or digestive diseases treated by anti-TNF agents (etanercept or infliximab) in patients with chronic C hepatitis have been reported (1). Inhibition of TNF is a recognized therapeutic option for psoriasis and does not seem to be deleterious for chronic C hepatitis (and could even be beneficial for some authors). The situation seems to be different for B hepatitis, since several cases of HBV reactivation with a case of fulminant hepatitis were reported under infliximab (2).

Thus, etanercept is an interesting therapeutic option in patients with severe psoriasis and chronic active C hepatitis.

REFERENCES

Appendix 8

Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-γ release assay vs. tuberculin skin test


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Accepted for publication
25 May 2009

Key words
adalimumab, etanercept, infliximab, psoriasis, T-SPOT.TB, tuberculosis

Conflicts of interest
None declared.

Presented at the 5th International Congress Psoriasis from Gene to Clinic, London, U.K., 4–6 December 2008 and awarded the poster prize.

Summary
Background Antitumour necrosis factor (anti-TNF) treatments may reactivate latent tuberculosis infection (LTBI). For detecting LTBI, the tuberculin skin test (TST) has low sensitivity and specificity. Interferon-γ release assays (IGRA) have been shown to be more sensitive and specific than TST.

Objective To compare the TST and the T-SPOT.TB IGRA for identifying LTBI in patients with psoriasis before anti-TNF treatment.

Methods A retrospective study was carried out over a 4-year period on patients with psoriasis requiring anti-TNF treatment. All were subjected to the TST, T-SPOT.TB and chest X-ray. Risk factors for LTBI and history of bacillus Calmette–Guérin (BCG) vaccination were recorded. The association of T-SPOT.TB and TST results with risk factors for LTBI was tested through univariate logistic regression models. Agreement between tests was quantified using kappa statistics. Treatment for LTBI was started 1 month before anti-TNF therapy when indicated.

Results Fifty patients were included; 90% had prior BCG vaccination. A positive T-SPOT.TB was strongly associated with a presumptive diagnosis of LTBI (odds ratio 7.43; 95% confidence interval 1.38–39.9), which was not the case for the TST. Agreement between the T-SPOT.TB and TST was poor, $\kappa = 0.33$ (SD 0.13). LTBI was detected and treated in 20% of the patients. In 20% of the cases, LTBI was not retained in spite of a positive TST but a negative T-SPOT.TB. All patients received an anti-TNF agent for a median of 56 weeks (range 20–188); among patients with a positive TST/negative T-SPOT.TB, no tuberculosis was detected with a median follow-up of 64 weeks (44–188). One case of disseminated tuberculosis occurred after 28 weeks of adalimumab treatment in a patient with LTBI in spite of treatment with rifampicin.

Conclusion This study is the first to underline the frequency of LTBI in patients with psoriasis (20%), and to support the use of IGRA instead of the TST for its detection. Nevertheless, there is still a risk of tuberculosis under anti-TNF therapy, even if LTBI is correctly diagnosed and treated.

Antitumour necrosis factor (anti-TNF)-α agents are approved for the treatment of psoriasis or other inflammatory diseases. However, they may reactivate latent tuberculosis infection (LTBI).¹,² Thus, screening for LTBI is mandatory and preventive treatment should be given to all patients with evidence of LTBI before starting any anti-TNF-α therapy,³ even if it does not offer complete protection.³ Screening for LTBI is traditionally based on history, chest X-ray and the tuberculin skin test (TST).¹,² However, the TST has disadvantages: a low specificity with false-positive results in bacillus Calmette–Guérin (BCG)-vaccinated subjects. This leads to unnecessary treatments for LTBI with a significant risk of drug toxicity, and lower sensitivity in immunosuppressed patients compared with healthy subjects resulting in false-negative results and a subsequent risk of tuberculosis reactivation with anti-TNF therapy. Finally, the limit above which the TST is considered positive (i.e. indicative of latent infection) differs according to countries and guidelines (5–10 mm).

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Since the early 2000s, in vitro blood tests measuring production of interferon (IFN)-γ by T cells exposed to antigens highly specific for Mycobacterium tuberculosis have been developed. These tests (T-SPOT.TB; Oxford Immunotec, Oxford, U.K. and QuantiFERON®-TB Gold; Cellestis, Carnegie, Australia), collectively referred to as IFN-γ release assays (IGRAs), are not affected by prior BCG vaccination, thus offering increased specificity compared with the TST. Their sensitivity, extrapolated from studies in patients with active tuberculosis, is probably at least as good as that of the TST in the detection of LTBI. Recent guidelines have integrated the use of IGRAs in screening strategies for subjects exposed to tuberculosis. The U.S. Centers for Disease Control and Prevention guidelines state that the QuantiFERON-TB Gold test can be used in all circumstances in which the TST is used and can be used in place of the TST. The U.K. National Institute for Health and Clinical Excellence 2006 guidelines and the 2007 Swiss national guidelines both recommend, for immunocompetent adults, a two-step procedure, i.e. confirmation of positive TST results using an IGRA.

However, there are few data on LTBI detection and use of IGRAs in patients with psoriasis. The aim of this study was (i) to determine the frequency of LTBI in a population of patients with psoriasis before anti-TNF treatment, (ii) to compare the TST with T-SPOT.TB for detecting LTBI, and (iii) to evaluate the tolerance and effectiveness of treatment for LTBI under anti-TNF therapy in our patients.

Materials and methods

This retrospective study was conducted in two academic dermatological centres (University Hospital, Geneva and CHUV, Lausanne). All patients seen between November 2004 and March 2008 with moderate to severe psoriasis qualifying for anti-TNF-α therapy were screened for LTBI with a chest X-ray, a TST and a T-SPOT.TB IGRA. The TST was considered positive if the induration diameter was ≥ 5 mm. There is no ‘gold standard’ test for the diagnosis of LTBI, we aimed to evaluate the risk factors for LTBI by recording the following data: age; country of origin and tuberculosis incidence in the country of origin according to World Health Organization data; history of tuberculosis exposure (family or work); history of prolonged stay in a high-incidence area; BCG vaccination; and prior immunosuppressive therapy (methotrexate, ciclosporin or efalizumab).

In the absence of a ‘gold standard’ for the diagnosis of LTBI, we analysed results of the T-SPOT.TB and the TST in relation to the risk factors for LTBI, BCG-vaccination status, and to a composite variable defining a probable diagnosis of LTBI (‘probable LTBI’) defined as having a history of definite exposure to a case of active tuberculosis and/or having a chest X-ray suggestive of prior tuberculosis infection (granulomas, calcified adenopathy) and/or originating from a high-incidence country (defined as > 40 cases in 100 000 per year).

The association of either T-SPOT.TB or TST results with risk factors for LTBI or BCG-vaccination status was tested through univariate logistic regression models. Agreement between tests was quantified using kappa statistics. All statistical analyses were performed with SPSS version 14.0, 2006 (Statistical Package for Social Sciences Inc., Chicago, IL, U.S.A.).

If LTBI was diagnosed, treatment with either rifampicin (10 mg kg⁻¹, max. 600 mg daily) for 4 months orisoniazid (5 mg kg⁻¹, max. 300 mg daily) for 9 months was started 1 month before introducing anti-TNF-α therapy, according to the Swiss guidelines.

Results

Fifty patients were analysed (Table 1). Ten patients (20%) came from or had lived in a country with a high incidence of tuberculosis. Forty-five patients (90%) had prior BCG vaccination.

Comparative results of tuberculin skin test and T-SPOT.TB

In 28 patients (56%), the TST and T-SPOT.TB were both negative. In eight patients (16%) both the T-SPOT.TB and TST (≥ 5 mm) were positive. Two cases had a negative TST but a positive T-SPOT.TB with a chest X-ray suggestive of LTBI (granuloma). In 12 cases (24%) the TST was positive and the T-SPOT.TB was negative; all had prior BCG vaccination and a normal chest X-ray. Agreement between both tests was poor for TST ≥ 5 vs. T-SPOT.TB: 36/50 (72%), κ = 0·33 (SD 0·13).

Probability of having a positive interferon-γ release assay or tuberculin skin test according to specific risk factors

Table 2 shows the association between the presence of risk factors for LTBI and results of an IGRA and TST based on univariate logistic regression analyses. Significant associations were found between having a positive T-SPOT.TB and probable LTBI, a chest X-ray suggestive of LTBI or a history of exposure to active tuberculosis. There was no association with age, previous immunosuppressive therapy or country of origin with a high incidence of tuberculosis. Conversely, none of the above-mentioned variables was associated with having a TST either ≥ 5 or 10. Association with BCG-vaccination status could not be tested, because of the high rate of patients vaccinated (90%). Results from the multivariable analysis (not shown) were not significant.

Latent tuberculosis infection diagnosis and treatment

A diagnosis of LTBI was considered in the 10 cases (20%) with a positive T-SPOT.TB. In 28 patients with both a negative TST and T-SPOT.TB, LTBI was considered as reasonably excluded. In 12 cases (24%) with a TST ≥ 5 but a negative T-SPOT.TB, all with a prior BCG vaccination and a normal X-ray, a diagnosis of LTBI was not considered.

A total of 12 patients were treated for LTBI (nine with rifampicin and three with isoniazid): the 10 patients with LTBI,
and two patients with a positive TST (≥ 5 mm) and a negative T-SPOT.TB but included in a clinical trial which did not accept the validity of T-SPOT.TB. There were no serious adverse effects with the LTBI treatment; two patients had an elevation of transaminase less than five times the normal limit, which did not require the interruption of therapy.

**Antitumour necrosis factor therapy**

Patients received anti-TNF-α therapy (etanercept, infliximab or adalimumab) for a median of 56 weeks (range 20–188). No case of tuberculosis occurred in the 10 patients with a positive TST/negative T-SPOT.TB who were not treated for LTBI, after a median duration of 64 weeks of anti-TNF therapy (range 44–188). A disseminated tuberculosis occurred after 28 weeks of adalimumab in a patient with LTBI treated with rifampicin for 4 months.

**Discussion**

The present study is to our knowledge the first to show that, in a population of patients treated for psoriasis, a positive T-SPOT.TB IGRA is strongly associated with the presence of risk factors for LTBI. This association was not found for the TST, and agreement between the T-SPOT.TB and TST was poor, probably because of a high rate of BCG-vaccinated patients (90%) acting as a confounding factor. As there is no gold standard for the diagnosis of LTBI, it was impossible to estimate the true sensitivity and specificity of either test in this setting.

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**Table 1 Characteristics of the 50 patients analysed**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 50)</th>
<th>T-SPOT.TB (n = 20)</th>
<th>TST ≥ 5 mm (n = 20)</th>
<th>TST ≥ 10 mm (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior immunosuppressive therapy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BCG vaccination, %</td>
<td></td>
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<td></td>
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<tr>
<td>Risk factors for LTBI, %</td>
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<td></td>
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</tr>
<tr>
<td>High TB incidence in country of origin</td>
<td></td>
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</tr>
<tr>
<td>Contact with TB patient (family or work)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chest X-ray suggestive of TB</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Probable LTBI†</td>
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</table>

**Table 2 Association of either T-SPOT.TB or the tuberculin skin test (TST) results with risk factors for latent tuberculosis infection (LTBI): univariate logistic regression models**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T-SPOT.TB</th>
<th>TST ≥ 5 mm</th>
<th>TST ≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (0.99–1.11)</td>
<td>0.99 (0.95–1.0)</td>
<td>1.01 (0.99–1.11)</td>
</tr>
<tr>
<td>Prior immunosuppressive therapy*</td>
<td>1.71 (0.31–9.3)</td>
<td>0.85 (0.24–2.97)</td>
<td>0.66 (0.18–2.36)</td>
</tr>
<tr>
<td>Risk factor for LTBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TB incidence in country of origin</td>
<td>2.02 (0.42–9.8)</td>
<td>2.78 (0.67–11.7)</td>
<td>2.07 (0.51–8.47)</td>
</tr>
<tr>
<td>Contact with TB patient (family or work)</td>
<td>5.67 (1.25–25.7)</td>
<td>2.14 (0.55–8.3)</td>
<td>1.67 (0.43–6.5)</td>
</tr>
<tr>
<td>Chest X-ray suggestive of TB</td>
<td>25.3 (2.41–267)</td>
<td>2.6 (0.39–17.4)</td>
<td>3.21 (0.48–21.4)</td>
</tr>
<tr>
<td>Probable LTBI†</td>
<td>7.43 (1.38–39.9)</td>
<td>3.0 (0.93–9.7)</td>
<td>2.08 (0.64–6.73)</td>
</tr>
</tbody>
</table>

CI, confidence interval. *Prior immunosuppressive therapy: methotrexate, ciclosporin or efalizumab. †Probable LTBI defined as having a history of definite exposure to a case of active TB and/or having a chest X-ray suggestive of prior TB infection (granulomas, calcified adenopathy) and/or originating from a country with a high incidence (defined as > 40 in 100 000 per year). Bold text: significant association (P < 0.01)
There are very few data concerning LTBI and the use of IGRA in patients with psoriasis. In a recent report of 11 patients, Desai et al.12 studied the utility of another IGRA (QuantiFERON) in screening for LTBI before anti-TNF therapy. They suggest that QuantiFERON should replace the TST for LTBI screening because its validity is well documented in rheumatological disorders, but there was no evaluation of risk factors for LTBI in the patients assessed.

We chose to base our diagnosis of LTBI on the results of the T-SPOT.TB rather than on the TST. Several points suggest that patients with LTBI were correctly identified: patients with a positive T-SPOT.TB had a significant association with risk factors for LTBI; and in 10 of 12 patients with a positive TST and a negative T-SPOT.TB, no treatment was given and no tuberculosis occurred under anti-TNF therapy with a mean follow-up of 76 weeks. According to the literature, most cases of tuberculosis in patients receiving anti-TNF therapy are detected within 12 months of the beginning of anti-TNF treatment.13 Treatment for LTBI was administered in 12 cases, and was avoided in 10 patients, whereas it would have been given to 22 patients if we had followed the guidelines based on the TST alone. Treatment for LTBI was relatively well tolerated, with a slight elevation of transaminases in two patients.

Twenty per cent of our patients had a probable LTBI which we consider to be a high rate; however, we were unable to compare our results with those from other studies, as published data only report the frequency of tuberculosis in patients under an anti-TNF agent for moderate to severe plaque psoriasis.6 In these studies, the patients were screened for LTBI and treated if necessary before the anti-TNF treatment, but the actual number diagnosed with LTBI, and the tolerance of its therapy are not reported.

An important message from our observations is that the risk of active tuberculosis under anti-TNF therapy persists even if LTBI is diagnosed and treated. Indeed, a case of disseminated tuberculosis occurred in a patient adequately treated for LTBI. Even if screening of LTBI reduces the occurrence of active tuberculosis under anti-TNF therapy,14 a residual risk remains, with atypical and disseminated presentations that dermatologists should be aware of.

Our study had a few limitations. It was retrospective in design, but as all patients seen in both institutions were analysed, the risk of selection bias was limited. Also, we included a relatively low number of patients, which may have limited the feasibility of certain statistical computations (i.e. multivariate logistic regression). However, the data presented are the first to show in this population highly significant univariate results between risk factors for LTBI and the T-SPOT.TB, and support the use of IGRA instead of the TST.

References


Appendix 9

CORRESPONDENCE

Eczematous drug eruption after infliximab

DOI: 10.1111/j.1365-2133.2004.06282.x

Sir, Infliximab (Remicade®, Schering-Plough), a humanized antitumour necrosis factor (TNF)-α monoclonal antibody, has been associated with several cutaneous side-effects.1–4 We report a patient with an eczematous eruption that appeared after the administration of infliximab.

A 36-year-old man presented with a diffuse pruritic rash of 1 week’s duration. He had been receiving treatment for 3 months with oral leflunomide 20 mg daily and intravenous infliximab 3 mg kg$^{-1}$ at weeks 0, 2 and 6 for a palmoplantar pustular psoriasis with severe arthritis. Four days after the third infusion of infliximab he developed a pruriginous maculopapulovesicular erythematous eruption of the limbs and trunk (Fig. 1a). There was no history of allergy or eczema. Abnormal laboratory results included elevated erythrocyte sedimentation rate at 35 mm in the first hour (normal < 10), white blood cell count of 15·1 × 10$^9$ L$^{-1}$ with 71% neutrophils and 1% eosinophils, and C-reactive protein at 49 mg L$^{-1}$ (normal < 10). Human immunodeficiency virus, syphilis and Chlamydia serology were negative and there was no evidence for any viral disease. Skin biopsy showed spongiform dermatitis with oedema in the epidermis between keratinocytes and the upper dermis, associated with keratinocyte necrosis, and a lymphocytic infiltrate in the upper dermis (Fig. 1b). The skin condition improved within 2 weeks after stopping the two drugs and the use of topical steroids. One month later, patch tests to leflunomide and infliximab were negative. As infliximab had been proving beneficial for the arthritic condition in this patient, rechallenge with a perfusion of 50 mg of infliximab was attempted. Two days later, the eczematous rash reappeared with an identical histological pattern. Thereafter, infliximab was switched to subcutaneous etanercept (Enbrel®, Wyeth), another TNF-α inhibitor, without recurrence of the rash.

TNF-α inhibitors are highly effective in the treatment of early and chronic rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease and psoriatic skin lesions.5 In clinical studies with infliximab, a humanized mouse monoclonal antibody against human TNF-α, adverse drug reactions were most frequently reported in the respiratory system (upper and lower respiratory tract infections), and in the skin and appendages.1 The most frequently described skin side-effects are mainly delayed hypersensitivity reactions: erythema multiforme, leucocytoclastic vasculitis, annular lichenoid eruption, lupus-like syndrome, bullous skin lesions6 and eczematide-like purpura.1–4,6 Several eczematous skin eruptions following infliximab have been reported previously.5,7 Skin reactions typically arise after one or several repeated treatments, and at 1–14 days after the injection.

In arthritic conditions, infliximab is classically given with methotrexate to reduce the incidence of human antichimeric

Figure 1. (a) First eczematous rash 4 days after the third infusion of infliximab in combination with leflunomide. (b) Histopathology confirmed a spongiform dermatitis associated with keratinocyte necrosis and a lymphocytic infiltrate in the upper dermis (haematoxylin and eosin; original magnification ×100).
antibodies. Methotrexate may be replaced by leflunomide in patients intolerant to methotrexate, but the combination of infliximab and leflunomide has been associated with a high frequency of adverse events. Kiely and Johnson reported a pruriginous rash in 14 of 20 rheumatoid arthritis patients treated with this combination. The skin reactions were characterized by eczematous patches with excoriation, and in some cases with lichenoid features.

Despite the fact that the molecule is well absorbed percutaneously, patch tests were negative in our patient, and only the rechallenge during a perfusion allowed us to confirm that infliximab was the cause of the eczematous rash. This led to discontinuation of infliximab. In one similar case, the dermatitis flared after each infliximab infusion, but responded to therapy with topical steroids and topical 0.03% tacrolimus.

Finally, we did not observe cross-reactivity between infliximab and etanercept. No eczematous eruption developed under etanercept therapy. Thus, this adverse effect appears to be related to the molecular structure of infliximab rather than being a consequence of TNF-α blockade, as both drugs share the similar purpose of TNF-α blockade, but have different structures, one being a humanized antibody and the other a fusion protein between the p75 human TNF-α receptor and a human immunoglobulin. However, an eruption with a pattern of erythema multiforme has been observed in a patient following treatment with both infliximab and etanercept, and this could be related to TNF-α blockade in this case.

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Endothelin-1 could be one of the targets of psoriasis therapy

DOI: 10.1111/j.1365-2133.2004.06277.x

Sir, All current treatments for psoriasis have limitations, particularly for severely affected patients. The pathogenesis of this inflammatory skin disorder that may affect about 1–3% of the world population is still under debate. One of the principal clinical aspects of psoriasis is the hyperproliferation of keratinocytes in some skin areas via the action of inflammatory mediators. Controlling this upregulated growth would be a very attractive therapy even if the causative agent(s) of the disease cannot be blocked. The active vitamin D₃ analogues tacalcitol, calcipotriol and maxacalcitol are examples of an effective treatment which addresses keratinocyte hyperproliferation without affecting the underlying cause of the disease.

Keratinocytes can produce cytokines and growth factors, and some of these can stimulate cell proliferation through an autocrine loop. Several years ago it was reported by our group that endothelin (ET)-1 is produced in keratinocytes and acts through the ET₄ receptor as an autocrine growth factor for these cells. ETs are a family of three vasoactive peptides, termed ET-1, ET-2 and ET-3, which induce their biological actions through at least two major receptor subtypes that belong to the family of G-protein coupled receptors: a selective ET₄ receptor, which binds ET-1 and ET-2 with high affinity and ET-3 with low affinity, and a nonselective ET₃ receptor which binds all ET isopeptides with equal affinity. It has recently been reported that compounds that antagonize the action of ET-1 by blocking the ET₄ receptor may control the growth of tumour cells in which the ET-1 autocrine loop is upregulated. High levels of ET-1 have been found in psoriatic skin and in the serum of patients with psoriasis. Inflammatory cytokines such as interleukin-1α increase the production of ET-1 that in turn may lead to the chronic stimulation of keratinocyte proliferation. Other growth factors and cytokines can also regulate the homeostasis of epidermal differentiation and proliferation, but nevertheless ET-1 seems to play an important role in these processes. To verify this hypothesis and in an attempt to evaluate possible new therapies for controlling skin proliferation in psoriasis, an ET-1 antagonist was administered to primary keratinocytes isolated from psoriatic patients as already reported. Briefly, keratinocytes were isolated on a lethally irradiated feeder layer of 3T3-J2 cells; for serial propagation, cells were cultivated in a serum-free keratinocyte medium and utilized for the experiments at the second passage. Keratinocyte cultures were derived from punch biopsies of lesional and normal-appearing skin of 11 patients with psoriasis, and from three nonpsoriatic control individuals undergoing plastic surgery. All the patients had discontinued local (steroids and keratolytic compounds) and/or systemic (mostly ciclosporin) therapy 1 month before the biopsy.

No difference was seen in the presence and expression level of ET-1 receptors as measured by a semiquantitative reverse

References


Appendix 10

Refractory Chronic Cutaneous Sarcoidosis Responsive to Dose Escalation of TNF-Alpha Antagonists

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Key Words
Sarcoidosis · Tumor necrosis factor α antagonists · Infliximab · Adalimumab · Dose escalation

Abstract
Cutaneous sarcoidosis may be a chronic disease with important morbidity requiring aggressive therapy. The efficacy of different anti-tumor necrosis factor α (anti-TNF-α) treatments in refractory cutaneous and systemic sarcoidosis has been reported previously. We report the first patient with chronic cutaneous sarcoidosis who responded to dose escalation of anti-TNF-α agents that have been ineffective at the standard dosage, illustrating that the optimal dosing regimen has still to be defined for this indication before considering difficult-to-treat patients as nonresponders. Our case report also illustrates that the fusion protein etanercept, even used at a high dosage, may be less effective for the treatment of cutaneous sarcoidosis than the monoclonal antibodies infliximab and adalimumab.

Case Report
A 37-year-old woman was suffering from stage 1 pulmonary and cutaneous sarcoidosis for 5 years. She developed a maculopapular erythematous plaque on the left cheek extending to the...
paranasal canthus (fig. 1), two erythematous nodules on the chin and the right cheek and multiple nodular lesions on both arms. The localization on the face was causing important psychological morbidity. She had previously been treated by topical and systemic steroids, tacrolimus 0.1% ointment (Protopic\textsuperscript{®}), methotrexate, chloroquine, thalidomide, and pentoxifylline with poor results. Thus infliximab (Remicade\textsuperscript{®}) treatment was initiated (induction therapy by an infusion of 5 mg/kg for a body weight of 85 kg at weeks 0, 2, and 6 followed by a maintenance therapy every other month for 5 infusions) which revealed insufficient efficacy (fig. 2), the patient presenting an extension and new lesions at the fourth infusion although stage 1 pulmonary sarcoidosis regressed during this therapy. Intralesional infliximab injections were performed in 4 lesions on the arm (6 mg total dose for 4 injections) with the hypothesis of a better local bioavailability, but this treatment was ineffective. The dosage and the frequency of infliximab infusions were increased (7.5 mg/kg every month) with an excellent clinical improvement maintained for 7 infusions (fig. 3). The treatment was interrupted at this moment on the patient’s request. After 4 months, the lesions relapsed and subcutaneous injections of etanercept (Enbrel\textsuperscript{®}), 50 mg twice weekly, were started for 3 months, without any clinical response. Adalimumab (Humira\textsuperscript{®}) was then introduced at a dosage of 40 mg every other week, combined with UVA1 therapy twice weekly for 3 months (23 sessions; total dose 595 J/cm\textsuperscript{2}). The clinical response was incomplete after 5 months and adalimumab was then increased to 80 mg every

Fig. 1. Maculopapular erythematous plaque of the left cheek extending to the paranasal canthus.

Fig. 2. Insufficient response after 5 infusions at a standard dosage of infliximab (5 mg/kg at weeks 0, 2, and 6 followed by an infusion every other month) – persistence of an inflammatory plaque surrounded by an infiltrated border.

Fig. 3. Excellent treatment response with a regression of the erythema and the infiltration after 7 months of infliximab with a dose escalation to 7.5 mg/kg every month.

Fig. 4. Excellent evolution 7 months after adalimumab treatment initiation at a dosage of 80 mg every other week.
other week. Clinical evolution was excellent with a clear reduction of the existing lesions and the absence of development of new sites persisting for 7 months under maintenance therapy (fig. 4).

Discussion

Tumor necrosis factor-α (TNF-α) plays a major role in infectious and noninfectious granuloma formation. Its implication has been studied in various systemic granulomatous diseases such as tuberculosis, sarcoidosis and Crohn’s disease [3]. In sarcoidosis, high levels of TNF-α are correlated with disease activity and progression [3]. Logically, the efficacy of TNF-α antagonists for the treatment of systemic and cutaneous sarcoidosis has been reported [4–9]. Infliximab and adalimumab are monoclonal antibodies directed against TNF-α that bind to free and cell surface TNF-α, while etanercept is a recombinant human TNF receptor fusion protein that antagonizes the effects of endogenous TNF-α by competitively inhibiting its interaction with cell surface receptors. Adalimumab and infliximab induce apoptosis of cells presenting the bound form of cell surface receptors. Adalimumab and infliximab have a better ability to disrupt granuloma than etanercept. There are clinical pieces of evidence to support this hypothesis, with a better activity of adalimumab and infliximab than etanercept in granulomatous disorders such as sarcoidosis and Crohn’s disease. Moreover, paradoxical development of noncaseating granuloma has been documented under anti-TNF agents and more frequently with etanercept, raising the hypothesis that TNF inhibitors may sometimes leave sufficient cytokine activation to support granuloma formation [11–14].

Our patient did not respond to standard doses of the three TNF inhibitors and a high dosage of etanercept, but she responded to high dosages of infliximab and adalimumab. There are no clear recommendations of anti-TNF use in cutaneous sarcoidosis. In several studies and reports, infliximab and adalimumab were administered based upon the conventional dose regimen for psoriasis. For example, in 54 patients suffering from lupus pernio, a dose regimen of 5 mg/kg infliximab at weeks 0, 2, and 6 followed by an infusion every other month appeared superior to systemic corticosteroids with or without additional agents [7]. In contrast to previous reports, our patient illustrates that the conventional anti-TNF dose regimen may not be sufficient in some patients with cutaneous sarcoidosis. The first treatment, infliximab, was administered at a weight-dependent dosage of 5 mg/kg based upon the conventional dose regimen for psoriasis. Major clinical effectiveness could nevertheless only be observed after a notable increase of the dosage to 7.5 mg/kg every month. We observed the same phenomenon with adalimumab, which was effective at the double dosage (80 mg every other week) of the conventional one used for psoriasis patients (40 mg every other week).

This concept of dose escalation with TNF-α inhibitors has been validated in several diseases such as rheumatoid arthritis, Crohn’s disease or uveitis [15–17] for patients unresponsive to conventional doses. The optimal dosage, duration of therapy, and long-term toxicity of TNF antagonists in patients with refractory sarcoidosis are yet to be determined. To our knowledge, our patient is the first case report illustrating the effectiveness of dose escalation of anti-TNF drugs for the treatment of refractory cutaneous sarcoidosis.

References


Appendix 11

Infliximab for Netherton syndrome: Sustained clinical improvement correlated with a reduction of thymic stromal lymphopoietin levels in skin

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INTRODUCTION
Netherton syndrome (NS) is a skin disease caused by mutations in the gene SPINK5, a gene encoding a protein called protease inhibitor LEKTI (lymphoepithelial Kazal-type-related inhibitor). Recent experimental data in vitro and in vivo have reported overexpression of TSLP (thymic stromal lymphopoietin), a cytokine pro-Th2 and pro-inflammatory cytokines such as TNF alpha in the epidermis of patients deficient in protein LEKTI (1). We report a case of Netherton’s syndrome with a cutaneous expression of high TSLP and TNF alpha, who presented a dramatic clinical improvement with the anti TNF monoclonal antibody infliximab.

OBSERVATION
We report the case of a 25-year old woman with a typical clinical NS, confirmed by the absence of LEKTI expression in the epidermis. She presented with recurrent severe inflammatory vesiculopustular cutaneous flares, unresponsive to therapy with systemic dapsone, topical steroids, tacrolimus and pimecrolimus. Thus, we initiated infliximab (monoclonal antibody against TNF-α) infusions at 5mg/kg with an induction therapy (week 0-2-6), followed by a maintenance therapy every other month. After the second infusion, a dramatic improvement was observed and after one year of therapy the skin was nearly clear of inflammatory lesion; however the ichthyosis was not improved.

We report a case of Netherton syndrome with a cutaneous expression of high TSLP and TNF alpha, who presented a dramatic clinical improvement with the anti TNF monoclonal antibody infliximab.

CONCLUSION
In our observation, high levels of TSLP skin were correlated with inflammatory activity of the disease, which is consistent with recent data (2) and indicates that this cytokine seems important in NS. Moreover, our data suggest that TNF may play a crucial role in NS and in the inflammatory cascade driven by TSLP, and that an anti-TNF should be considered as a therapeutic approach for NS.