

## LETTERS TO THE EDITOR

## Exacerbation of Psoriasis after Treatment with an EGFR Tyrosine Kinase Inhibitor

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Sir,

Epidermal growth factor receptor (EGFR), also known as HER-1 or erbB-1, is one of the four members of the erbB/HER EGFR family, located in the cytoplasmatic membrane, which play a key role in the regulation of normal cell growth and differentiation. They consist of an extracellular ligand-binding domain, a transcellular lipophilic segment that anchors the receptor in the cell membrane and an intracellular domain with a tyrosine kinase activity. The binding of the ligand to the extracellular part of the receptor results in the pairing of the receptor with another EGFR (homodimerization) or with another member of erbB family (heterodimerization). Homo- or hetero-dimerization leads to the phosphorylation of the intracellular tyrosine kinase that activates a signal transduction cascade to the nucleus, stimulating cell division, cell proliferation, cell adhesion and also angiogenesis and protection from apoptosis (1).

Inhibitors of the EGFR family and its tyrosine kinase have recently emerged as promising novel agents for the treatment of human malignancies (1). Recently, the intracellular tyrosine kinase inhibitor (TKI) ZD-1839 has gained approval by the FDA for the treatment of non-small cell lung cancer (2). There is growing evidence that EGFR tyrosine kinase may also play a key role in non-malignant diseases like papilloma virus infections (3), inflammatory conditions (4) and psoriasis (5). Hyperproliferation of keratinocytes is implicated in the pathogenesis of psoriasis and TKIs have been considered as potential antipsoriatic agents. Indeed in organ cultures, where normal skin was exposed to growth factor-enriched culture medium, normal skin exhibited abnormal histological features compatible with that of psoriatic skin. In contrast, when organ cultures of psoriatic skin were incubated with a monoclonal antibody against the EGFR, regression of the psoriatic phenotype was noted (6). So far two quinazolines from the family of TKIs, AG1478 and its bromoanalogue AG1517/SU5271 have been studied *in vitro* on psoriatic keratinocytes, and the results imply that SU5271 inhibits EGFR autophosphorylation and consequently EGF-driven DNA replication, resulting in the inhibition of cell proliferation of psoriatic keratinocytes (7). SU5271 is currently being evaluated in phase I clinical trials in psoriatic patients.

We report here a case of exacerbation of psoriasis in a patient with lung cancer who was treated with an EGFR TKI.

## CASE REPORT

A 69-year-old male patient was diagnosed with a stage IV squamous cell lung cancer. The patient had a history of plaque-type psoriasis involving the palms, elbows, knees and nails. His disease had been treated in the past with several topical regimens. At the time of the diagnosis of lung cancer the psoriatic lesions were in stable condition and were treated, as usually, with topical emollients and occasional medium-potency topical corticosteroids.

He received six courses of chemotherapy with carboplatin and gemcitabine with stabilization of his lung disease. He was further treated with ZD1839 (Iressa<sup>®</sup>). The drug was administered orally at a dose of 250 mg daily. After 1 month of treatment there was worsening of the existing psoriatic lesions, while new lesions developed on the soles of the feet. Arthritis of the distal interphalangeal joints was also noted. Treatment with ZD1839 was discontinued. There was rapid improvement of the psoriatic lesions and a month later his psoriasis had returned to its initial appearance prior to treatment with ZD1839.

## DISCUSSION

Psoriasis is a chronic inflammatory skin disease characterized by dysregulation of keratinocyte cell growth, local immune activation, local inflammation and altered microvascular structure. There is strong evidence that in psoriatic cells the homeostatic mechanisms are disrupted and the balance between growth regulatory signals and receptor expression is altered. EGFR is widely expressed in the basal layer of the epidermis in normal skin but its distribution appears to be altered in psoriatic epidermis, where it is also expressed in the upper keratinocyte layers (8). Moreover, one of its ligands, transforming growth factor- $\alpha$  (TGF $\alpha$ ) is overexpressed in psoriatic epidermis compared with normal keratinocytes (7). The result of this overexpression may contribute to the activation of epidermal keratinocyte proliferation, which is the hallmark of psoriasis.

Interestingly, the evidence suggesting a potential therapeutic effect of EGFR TKIs in psoriasis is in conflict with the deterioration of the disease observed in our case. ZD1839 (Iressa) is a selective EGFR TKI that is currently being evaluated in clinical trials in various cancers. It is highly selective in the inhibition of the intracellular tyrosine kinase region, blocking EGFR downstream signal transduction pathways, which induce cell cycle arrest, inhibit angiogenesis, decrease proliferation and increase apoptosis. ZD1839 has been associated with skin toxicity in a significant percentage of patients (8). The most common manifestation of such toxicity is an acneform rash, the mechanism of which has not yet been elucidated. Nevertheless, there are no clinical data on the effect of treatment with ZD1839 on psoriatic patients. In our case, the psoriasis was in a stable condition for many years and there was no exposure to any of the known exacerbating factors of the disease at the time of the event. No precipitating illness, trauma or emotional distress were reported and the patient denied any intake of excessive amounts of alcohol. There was also no change in the topical treatment of his disease. In addition, lung cancer has not been associated with psoriatic flares. The possibility of an exacerbating effect caused by the cessation of cytostatic agents, particularly gemcitabine, which has been shown to improve psoriasis temporarily (9), should be taken into consideration. Nevertheless, there was no improvement of psoriasis with gemcitabine and no flare after its discontinuation until ZD1839 was started. Therefore, although a possible effect of gemcitabine treatment cannot be excluded, we believe that this is unlikely. However, the fact that exacerbation of psoriasis occurred shortly after the initiation of treatment with ZD1839 and regressed rapidly after its cessation without other treatment, strongly supports the causative role of this agent. The underlying mechanisms of this observation cannot be readily explained by the currently available data. A recent study showed that EGFR expression in normal keratinocytes was not modified after treatment with ZD1839 in paired skin biopsies obtained before and during therapy (8). On the other hand, foci of

parakeratosis were noted in samples from treated patients (8). Furthermore, recent animal studies have shown that TKIs may stimulate cytokine production, which might result in altered cutaneous immune response (10). It can be speculated that in certain cases induction of parakeratosis and cytokine production may predominate over the anti-proliferative action of ZD1839.

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