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Letter to the Editor

Erlotinib and Gefitinib, Epidermal Growth Factor Receptor Kinase Inhibitors, May Treat Non-Cancer-Related Tumor Necrosis Factor-α Mediated Inflammatory Diseases

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A recent report from the National Institutes of Health discussed the potential role of kinase inhibitors in the treatment of immune-mediated diseases [1]. Blocking kinases may be an effective way to block immune cell activation and in turn treat autoimmune disease. Protein kinases are fundamental components of diverse signaling pathways, including immune cells. At present, 13 kinase inhibitors have been approved in the U.S., all for oncologic indications. However, various other kinase inhibitors are now in clinical trials for autoimmune diseases, including psoriasis, inflammatory bowel disease, and rheumatoid arthritis.

Receptors for cytokines, such as tumor necrosis factor-α, are not directly associated with kinases, but they link to downstream kinase cascades. It is possible that kinase inhibitors that enter clinical use as treatments for cancer may have off-target effects, making them efficacious in the treatment of autoimmune diseases. Erlotinib and gefitinib, used to treat non small cell lung cancer, are kinase inhibitors of the epidermal growth factor receptor tyrosine kinase domain, and they may also function as immunomodulatory drugs. This article reports on their potential for treating the autoimmune diseases psoriasis, inflammatory bowel disease, and rheumatoid arthritis, as well as other nonautoimmune inflammatory disorders.

CASE REPORT

A 73-year-old nonsmoker male urologist was well until June 2011, when he developed severe back pain. Evaluation revealed non-small cell lung cancer (NSCLC) metastatic to multiple vertebrae, lymph nodes, and the liver. Pathology was consistent with a moderately differentiated adenocarcinoma with epidermal growth factor receptor (EGFR) mutations in L858R in exon 21 and S7681 in exon 20. Erlotinib, 150 mg daily, was initiated as sole therapy. After 3 weeks, his back pain abated. After 15 months, he remains asymptomatic and his cancer remains in remission.

The patient also had a greater than 10-year history of mild plaque psoriasis on both elbows that was unresponsive to topical treatment and of insulin-dependent, insulin-resistant type 2 diabetes mellitus associated with metabolic syndrome. Three weeks after initiating erlotinib, his psoriasis completely cleared. After 15 months, there is no evidence of recurrent psoriasis. After 10 weeks of erlotinib, the patient no longer required insulin [2]. He remains off insulin, takes no medication to reduce insulin resistance, and in spite of minimal weight loss, takes only oral glimepiride 2 mg b.i.d. to stimulate insulin secretion. His A1C is less than 6.5%.

DISCUSSION

Psoriasis, an autoimmune disease, and insulin resistance associated with metabolic syndrome, a nonautoimmune inflammatory condition, share a commonality in that both are mediated through tumor necrosis factor (TNF)-α. TNF-α is a proinflammatory cytokine that contributes to the acute phase response. TNF-α is mainly secreted by macrophages and acts on the target tissue via TNF receptor (TNFR)-1 and TNFR2 to induce apoptotic cell death, cellular proliferation, differentiation, and inflammation. Overproduction of TNF-α has been implicated in a variety of autoimmune and nonautoimmune inflammatory diseases [3]. Erlotinib and gefitinib appear to have a secondary mechanism of action as TNF-α inhibitors [2, 4], capable of treating non-cancer-related TNF-α mediated inflammatory autoimmune and nonautoimmune conditions.

Our patient also had a second autoimmune disease, Hashimoto thyroiditis (HT). HT is a T-cell-mediated condition that affects the thyroid gland producing hypothyroidism. Macrophages infiltrate the thyroid gland injuring thyrocytes, releasing proteins and inducing production of antibodies to thyroid peroxidase, an enzyme involved in the production of thyroid hormones. TNF-α plays a major role in the destruction of thyrocytes. Antithyroid peroxidase antibodies cause depletion of thyrocytes via apoptotic mechanisms of cytotoxity [5]. There is no known treatment for HT and the resulting hypothyroidism is managed with thyroid replacement. Normal serum levels of antithyroid peroxidase antibodies are 0–60. With HT, levels can be elevated to greater than 10,000. In 2007, the patient had a level of 1,719. One year after starting erlotinib, his level was reduced by 79% to 366, suggesting an anti-TNF-α erlotinib effect.

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Psoriasis is a skin disorder characterized by sharply demarcated chronic erythematous plaques covered by silvery white scales, most commonly appearing on the elbows, scalp, and torso. The plaques of psoriasis are the result of epidermal hyperproliferation with abnormal cellular maturation [6]. In psoriatic epidermis, the EGFR is overexpressed in the supra basal layer with a two-fold increase in EGFR binding capacity compared with similar thickness normal skin. This suggests that EGFR inhibition can control psoriasis, but this conclusion may not be accurate.

A recognized side effect of EGFR inhibition is a moderate papulopustular eruption on the face, scalp, and torso. The EGFR is expressed in epidermal keratinocytes, sebaceous glands, and hair follicle epithelium. The mechanism that underlies the EGFR inhibitor-associated cutaneous toxicity is incompletely characterized, but interference with the follicular and intrafollicular epidermal growth signaling pathway is considered crucial [7].

A paradox exists as to how EGFR inhibition can produce cutaneous toxicity while producing clearing of psoriasis. The likely explanation is that clearing of psoriasis is not the result of EGFR inhibition, but that erlotinib resolves psoriasis through the immune system by inhibiting TNF-α. This conclusion is reinforced by the observation that biologic TNF-α antagonists such as adalimumab, etanercept, and infliximab are effective in treating psoriasis [8].

To date, the quest to find a clinically effective small-molecular-weight oral inhibitor with sufficient affinity to block TNF/TNFR interactions has not been successful. Erlotinib and gefitinib may be such agents. The kinase inhibitors erlotinib and gefitinib are chemically quinazoline derivatives. Compounds belonging to this family are reported to possess analgesic and anti-inflammatory properties, and certain derivatives have been demonstrated to have inhibitory activities toward both TNF-α production and T-cell proliferation [9].

Psoriasis, an autoimmune disease, has a primary T-lymphocyte based immunopathogenesis. T cells are involved in overall cell mediated immunity. Activated T lymphocytes produce TNF-α, a proinflammatory cytokine. Erlotinib inhibits T-cell proliferation and activation and has an immunosuppressive effect on T lymphocytes. It inhibits secretion of the proinflammatory cytokines of activated T cells [10], which include TNF-α. Erlotinib appears to resolve psoriasis through an effect mediated via the immune system rather than by inhibition of the EGFR.

Insulin resistance associated with obesity and metabolic syndrome is a nonautoimmune inflammatory condition [11]. Visceral fat is the source of proinflammatory cytokines including TNF-α [12], and overexpression of TNF-α has been implicated in the pathophysiology of insulin resistance. Erlotinib appears to reduce insulin resistance by possibly inhibiting TNF-α.

Crohn's disease is an autoimmune, chronic inflammatory disease of the intestine. In patients with Crohn's disease, mucosal levels of TNF-α and inflammatory cell production of TNF-α are elevated [13]. Therapy with monoclonal antibodies that inhibit TNF-α, such as infliximab and adalimumab, lead to a rapid reduction in inflammation and healing in many patients. Research suggests that erlotinib and gefitinib may be of benefit in treating Crohn's disease [14]. Erlotinib has also been demonstrated to inhibit progression to dysplasia in a colitis associated colon cancer model [15]. Patients with ulcerative colitis and Crohn's disease have an increased risk of developing colorectal cancer. Colorectal cancer associated with inflammatory bowel disease results from dysplasia and TNF-α has been identified as a crucial mediator of the initiation and progression of dysplasia [16]. TNF-α appears to promote cancer development through induction of gene mutations [17].

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder that principally attacks synovial tissue. The process involves an inflammatory response of the synovial capsule around joints, causing swelling, and often leads to destruction of articular cartilage and joint fusion. Synovial macrophages produce TNF-α. They also produce interleukin (IL)-1, another distinct proinflammatory cytokine [18]. The role of TNF-α and IL-1 in RA overlap, but TNF-α appears to be more important in producing inflammation and IL-1 more important in promoting cartilage and bone destruction [19].

In some patients, biologic TNF-α blockers such as adalimumab, etanercept, and infliximab produce a rapid deceleration of disease progression [20]. Blockade of IL-1 can also produce significant improvement. Anakinra, a recombinant human IL-1 receptor antagonist, blocks the biologic activity of IL-1, reducing inflammation and cartilage degradation [21], but it is less efficacious than the biologic TNF-α blockers [22]. There is a therapeutic rational for combined TNF-α and IL-1 blockade in treating RA [23], although the particular combination of anakinra with etanercept was associated with an increased incidence of serious infections [24]. In addition to erlotinib and gefitinib appearing to inhibit TNF-α, evidence indicates they have an off-target effect of inhibiting the IL-1 signaling pathway [25]. Consequently, erlotinib and gefitinib may be more effective than current biologic treatments for RA by simultaneously inhibiting TNF-α and IL-1.

Osteoarthritis (OA), also known as degenerative arthritis or degenerative joint disease, is neither an autoimmune nor a primary nonautoimmune inflammatory disease, but rather a condition resulting from a mechanical joint disorder that initiates erosion of articular cartilage and subchondral bone. Symptoms may include joint pain, tenderness and stiffness. When bone surfaces become less well protected by cartilage, bone may be exposed and damaged. TNF-α and IL-1 have been implicated in the pathophysiology of synovial inflammation and joint cartilage erosion in OA [26, 27]. Inflamed synovial membranes and chondrocytes secrete proinflammatory cytokines, including TNF-α and IL-1, and control the degeneration of the articular cartilage matrix [28]. Disease modifying antiosteoarthritis drugs are not available, but studies using subcutaneous injections of adalimumab [29] and intra-articular hand injections of infliximab [30], both biologic TNF-α inhibitors, reduced pain and slowed progression. Gefitinib may be an option in the treatment of osteoarthritis [31].

In addition to the reported observations involving psoriasis, type 2 diabetes associated with metabolic syndrome and Hashimoto thyroiditis, three case reports have been identified in the medical literature in which unrecognized inhibition of TNF-α by erlotinib or gefitinib is the most likely explanation for the improvements observed:

1. A 58-year-old man with stage IV NSCLC and a 35-year history of extensive psoriasis was placed on erlotinib. Four months after beginning erlotinib, the psoriasis had completely cleared [32].
2. A 72-year-old woman with stage IV NSCLC and a 2-year history of non-insulin-dependent type 2 diabetes associated with obesity and probable metabolic syndrome was placed on erlotinib. Within 4 weeks, she developed frequent episodes of hypoglycemia. Her diabetic medications were significantly reduced; after 8 months, her A1C decreased from 8.2% to 6.5% [33].
3. A 72-year-old woman with stage IV NSCLC and osteoarthritis was placed on gefitinib. After 2 weeks, she noted a marked improvement in her arthritic symptoms of pain and stiffness. When gefitinib was temporarily discontinued because of diarrhea, the symptoms returned. Once gefitinib was restarted, improvement returned. After 3 years, she had no evidence of tumor activity and continued to enjoy marked improvement in her arthritic symptoms [31]. Gefitinib has been demonstrated to suppress the TNF-α and IL-1 signaling pathways.

Conclusion

The process of obtaining marketing approval for new drugs can take more than 10 years and cost more than $1 billion. Medication repurposing—the practice of using old drugs in new ways—is faster and more affordable. Newer uses of previously approved drugs require considerably fewer resources because information about pharmacology and safety has previously been determined. One method of identifying potential new uses is through the observation of positive, unanticipated off-target effects during clinical use. Based upon the described observations, clinical trials are warranted to further evaluate erlotinib and gefitinib as potential immunomodulatory drugs.

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