Rev Med Hosp Gen Méx. 2016;79(1):26–32

REVISTA MÉDICA DEL
HOSPITAL GENERAL
DE MÉXICO
www.elsevier.es/hgmx

REVIEW ARTICLE

Off-label uses of etanercept in dermatology

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Received 31 August 2015; accepted 21 October 2015
Available online 9 December 2015

KEYWORDS
Etanercept;
Skin disease;
Treatment

Abstract Tumour necrosis factor alpha (TNFα) is a key molecule involved in the inflammatory response and thus related to the pathogenesis of several autoimmune and autoinflammatory diseases.

The blockade of TNF receptor (etanercept main effect) has been successfully used in psoriasis and psoriatic arthritis, among other rheumatologic diseases. The only approved indication for etanercept in dermatological disease is plaque psoriasis; however, the literature is full of case reports and case series where etanercept was used off-label, sometimes successfully. We review some of these indications.

PALABRAS CLAVE
Etanercept;
Enfermedad cutánea;
Tratamiento

Usos no aprobados de etanercept en Dermatología

Resumen El factor de necrosis tumoral alfa (FNTα) es una molécula clave en la respuesta inflamatoria y se relaciona con la patogenia de varias enfermedades autoinmunes y autoinflamatorias.

El bloqueo del receptor del FNTα (efecto principal del etanercept), ha sido utilizado con éxito en psoriasis y artritis psoriásica, así como en otras enfermedades reumatológicas. La única indicación aprobada para el uso de etanercept en padecimientos dermatológicos es en psoriasis en placa; sin embargo, la literatura está plena de reportes de casos y series de casos donde se utiliza etanercept con indicaciones no aprobadas en algunas ocasiones con éxito. Realizamos una revisión de algunas de tales indicaciones.

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http://dx.doi.org/10.1016/j.hgmx.2015.10.005

Introduction

Tumour necrosis factor alpha (TNFα) is a proinflammatory mediator involved in several cellular functions, primarily proliferation, differentiation and apoptosis.[1] Elevated levels of this cytokine are associated with excessive inflammation and severe organ injury,[2] and it is also involved in the pathogenesis of several autoinflammatory and autoimmune diseases. This has led to the development of TNFα agonists.

TNF is produced by various different cells, including mast cells, macrophages, fibroblasts and keratinocytes.[2]

Etanercept is a fusion protein that acts as a TNFα inhibitor. Structurally, it is a dimer of the extracellular portion of human TNFR2 fused to the Fc-portion of human IgG1, and inhibits both soluble and transmembrane TNFα.[1,3] Etanercept acts as a competitive inhibitor of TNFα[4] by binding TNFα and preventing its interaction with the cell surface receptor.[5]

Etanercept also binds to soluble TNF by interacting with a single soluble TNF trimer to produce 1:1 complexes. It is administered subcutaneously, and has an estimated bioavailability of between 58% and 63% and a half-life of 70 h.[2]

No drug interactions have been reported with etanercept because it is metabolised by proteolytic processes and eliminated in bile or urine.[2]

So far, it has been approved by the FDA (*Food and Drug Administration*) for inflammatory diseases such as moderate to severe rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, moderate to severe plaque psoriasis, psoriatic arthritis and juvenile idiopathic arthritis.[1,6,7] In dermatological diseases, it is only approved for moderate to severe recalcitrant or recurrent plaque psoriasis. Randomised, comparative, multicentre studies have shown etanercept to be safe and effective in various therapeutic regimens.[8] It is usually administered subcutaneously at a dose of 50 mg twice weekly, which can later been tapered to 25 mg twice weekly.[3,8]

Other TNFα inhibitors include infliximab, adalimumab, and more recently, certolizumab and golimumab.

These drugs have so far proved to be safe. However, the main concern is the development of opportunistic infections and reactivation of latent tuberculosis infection.[1] In a recent study, Guarneri and Polimeni[9] describe a case of Nicolau syndrome following administration of etanercept, a complication that should be borne in mind and treated promptly at the first sign of symptoms.

Etanercept is usually well tolerated, with the most common adverse effect being injection site pain, reported in 40% of patients.[3] Others frequently mentioned include a predisposition to respiratory infections (35%) and headache (20%).[5] Reactivation of latent tuberculosis has also been reported with long-term use of etanercept, together with lymphomas. Evidence of the latter, however, is inconclusive.[3] Other reactions reported are demyelinating disease of the central nervous system, aplastic anaemia, pancytopenia, onset or exacerbation of erythematous lupus, and sepsis.[5] Sepsis in this context has been studied extensively by Díaz-Lagares et al.,[10] in 344 patients with autoimmune disease receiving biological treatment. Of all the biological agents studied, the authors found that rituximab was associated with the highest risk for developing severe infection, and etanercept with the lowest.

Etanercept is contraindicated in patients with a history of hypersensitivity to any of its ingredients and with any level of active tuberculosis.[3]

An increasing number of studies report good results for the off-label use of etanercept to treat dermatological diseases, and this has prompted us to undertake this review, Table 1 lists the off-label indications in dermatology[7] and the regimens most commonly used in the studies reviewed.

Pemphigus vulgaris

Pemphigus vulgaris is a bullous autoimmune disease characterised by autoantibodies that target different antigens, primarily desmogleins 1 and 3, which are adhesion molecules in the desmosomes of keratinocytes.[5] TNFα is strongly associated with the pathogenesis of this condition,[4] and evidence has shown levels of this cytokine in serum and blister fluid to be associated with the clinical activity of the disease.[5]

Etanercept has been successful in treating pemphigus vulgaris, and its use is justified by the significant involvement of TNF in the development of acantholysis.[11]

A number of studies and case series have reported the use of etanercept in the management of recurrent and/or recalcitrant pemphigus vulgaris. In these cases, the drug was used either alone or in combination with systemic immunosuppressants such as systemic steroids, azathioprine, methotrexate, dapsone and IV immunoglobulin. The disease was successfully controlled within 3–6 weeks of treatment, with a reduction in the number of bullae and fewer recurrences.[3–5]

In a recent report published by Fiorentino et al.,[4] 6 patients with severe pemphigus vulgaris were included in a double-blind, randomised, placebo controlled study and treated with etanercept 50 mg twice weekly.

In another study, Tirado-Sánchez et al.,[12] describe 4 cases in which recalcitrant pemphigus vulgaris was treated successfully with etanercept and methotrexate.

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PPR) is an inflammatory disease of unknown aetiology, characterised by follicular hyperkeratosis and palmoplantar keratoderma that can progress to erythroderma in some cases. Opinions vary on the best treatment for PPR; only a few case studies and series have been reported, and the therapeutic approach is at the discretion of the attending specialist, based on severity. Some of the most effective treatments include oral retinoids (acitretin), methotrexate and PUVA therapy. A new approach with promising results involves the use of TNFα antagonists. In a recent study, Garcovich et al.,[13] investigated 7 patients with PPR (6 with type 1 and 1 with type 2) that had responded poorly to different systemic therapy regimens. Three patients were started on IV infliximab 5 mg/kg administered at week 2, week 6, and then weekly; 4 patients were started on etanercept 50 mg weekly. The primary outcome measure, 75% improvement, was achieved with the 6 type 1 patients. The type 2 patient presented partial recurrence.