Etanercept and ophthalmic herpes

Sarah Watson, Uppsala Monitoring Centre and Dr. Eugène van Puijenbroek, the Netherlands Pharmacovigilance Centre Lareb

Summary

Adverse reactions of etanercept such as opportunistic infections and eye inflammation are mentioned in the patient information leaflet and herpes zoster is included in the label. The risk of acquiring a herpes infection in the eye and the potential severity of that infection is however not mentioned in the patient information leaflet of etanercept. Information about the risks of ophthalmic herpes is important for an early diagnosis, as more severe forms of ophthalmic herpes can, if left untreated, permanently affect the eyesight.

Introduction

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary mammalian expression system. It is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis and psoriasis.[1]

Herpes zoster (shingles) is a common disorder in primary care and is caused by the Varicella-Zoster Virus (VZV). One fifth of the population, mainly elderly people, will present with this neurocutaneous infection during their lifetime. Most immunocompetent patients will experience spontaneous and complete recovery within a few weeks. Some, however, will develop complications such as post-herpetic neuralgia and, in cases of ophthalmic herpes zoster, sight-threatening eye problems.[2] A related DNA virus is Herpes Simplex Virus (HSV), that infects humans by direct contact of skin or of mucous membrane with lesions or secretions holding viruses. HSV type 1 is primarily responsible for orofacial and ocular infections and may cause ophthalmic herpes without the need for a primary ocular HSV infection. HSV type 2, which is generally transmitted sexually will only rarely infect the eye if orofacial contact is made with genital lesions, and is sometimes transmitted to neonates as they pass through the birth canal of a mother with an active genital HSV type 2 infection.[3]

Conjunctivitis is seen in nearly all ophthalmic herpes zoster patients. More severe disorders include keratitis, uveitis and optic neuritis. Untreated, these latter diagnoses might lead to permanently affected eyesight. Without an early diagnosis of ophthalmic herpes and subsequent antiviral treatment, about half of all patients will develop eye disorders of various kinds.[2] Both VZV and HSV may cause severe corneal infections. Although the pattern of the corneal manifestations differs, both types of herpes keratitis may result in potentially devastating complications for which immediate ophthalmological treatment is needed.[4,5] For HSV, as well as for HZV, the incidence of infections is increased in immunocompromised persons.[6]

Literature and Labelling

In the section for adverse reactions in the UK Summary of Product Characteristics for etanercept, herpes zoster is mentioned under serious infections; "*opportunistic infections have been reported in association with etanercept, including invasive fungal, parasitic (including protozoal) and viral (including herpes zoster)...*". Herpes simplex is not mentioned in the label.[1] However, due to the immunosuppressive nature of etanercept, reactivation of this virus is not unlikely.

The patient information leaflet for the same product under "Serious side effects" states that you may need urgent medical attention if you show "*signs of nerve disorders, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg*" and infections are listed as common. Under "Uncommon" side effects *eye inflammation* (not further specified) is given, and under "Rare" side effects *nervous system disorders* (... *inflammation of the nerves of the eyes...*) is listed.[7] However, for a patient, this information might seem unspecific and may not be perceived as a sign of a potentially serious ophthalmological disorder, with the risk of permanent damage.

Reports in VigiBase

As of 3 May 2018, there were 50 reports of ophthalmic herpes for etanercept in VigiBase, the WHO global database of individual case safety reports. Based on the overall reporting of adverse reactions for etanercept and on the adverse reaction ophthalmic herpes on its own in VigiBase, 4.1 reports were statistically expected for the drug–adverse drug reaction (ADR) combination

based on the disproportionality measure (IC). The reports originated from Europe and the US. Forty-five reports were classified as serious. Several ophthalmic disorders were co-reported, all in patients with a non-specified ocular herpes infection. These concerned a 39-year-old male with ulcerative keratitis, an 85-year-old female with a retinal haemorrhage, corneal scar and uveitis, a male, age not reported, who experienced a corneal graft rejection, a 48-year-old male with uveitis, corneal disorder and necrotising scleritis that needed a scleral patch graft, a consumer report concerning a 60-year-old woman who co-reported cataract and glaucoma, a consumer report concerning a female of unknown age with glaucomatocyclitic crisis (Posner-Schlossman Syndrome) and finally one consumer report concerning a male, age not reported, with recurrent ophthalmic herpes resulting in a corneal scar outside visual field. With the exception of glaucomatocyclitic crisis, the co-reported terms may result either directly or indirectly from an ophthalmic herpes infection.

Of the 24 cases with a documented outcome, 13 reports stated that the patients had *Not Recovered* from the event at the time the report was submitted, one *Recovered with sequalae*, seven reported that they had *Recovered* and three were *Recovering* at the time of reporting. Some reports also describe the situation of the patients. In one case, the patient stopped the treatment on their own initiative, after a severe episode of cold sores in the mouth, nose and ears, which was co-reported with "cold sores in the eye". On the other hand, two patients are described as requesting continued treatment despite serious adverse reactions, since the treatment was working so well. One patient did not consider the ophthalmic herpes to be serious.

Conclusion

Although infections and eye inflammation are listed in the patient information leaflet for etanercept, without clear information about the risk of acquiring ophthalmic herpes and more specifically, the risks of leaving it untreated, there is a risk of permanent damage to the sight of the patients who are not treated in time.

References

1. electronic Medicines Compendium: Summary of Product Characteristics for etanercept (Benepali). Available from: https://www.medicines.org.uk/emc/product/2708/smpc. Accessed: May 2018

2. Opstelten W, Zaal MJ. Managing ophthalmic herpes zoster in primary care. BMJ. 16 Jul 2005;331(7509):147-151.

3. Wang JC. Herpes Simplex Virus (HSV) Keratitis. Available from: https://emedicine.medscape.com/article/1194268-overview. Accessed: June 2018.

4. Li JY Herpes zoster ophthalmicus: acute keratitis. Curr Opin Ophthalmol. 2018 Jul;29(4):328-333.

5. Kalezic T, Mazen M, Kuklinski E, Asbell P. Herpetic eye disease study: lessons learned. Curr Opin Ophthalmol. 2018 Jul;29(4):340-346.

6. JT Schiffer, L Corey. Herpes Simplex Virus. Ch 136 1943-62. AND RJ Whitley. Varicella-Zoster Virus. Ch 137 1963-69. In: Mandell, Douglas, and Bennett's Principles and Practice of infectious diseases. Edited by GL Mandell, JE Bennett, 7th ed. Churchill Livingstone Elsevier, Philadelphia 2010 ISBN-978-0-4430-6839-3.

7. electronic Medicines Compendium: Patient information leaflet for etanercept (Benepali). Available from: https://www.medicines.org.uk/emc/files/pil.2708.pdf. Accessed: May 2018.