

1.1. Adalimumab and neuroendocrine carcinoma of the skin

Introduction

Adalimumab (Humira[®]) is a fully human recombinant monoclonal immunoglobulin G1 antibody expressed in Chinese hamster ovary cells. Adalimumab binds specifically to Tumor Necrosis Factor- α (TNF- α) and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors [1].

Adalimumab was granted marketing authorization on 8 September 2003 in Europe. Therapeutic indications include *rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis*. In the first three indications adalimumab is used either as monotherapy or in combination with methotrexate in patients with an inadequate response to classic disease-modifying anti-rheumatic drugs. In the other indications adalimumab is given to patients who have had an inadequate response to conventional therapy (ankylosing spondylitis), a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant (Crohn's disease) or to other systemic therapy including cyclosporine, methotrexate or PUVA (psoriasis). Adalimumab is available as Humira[®] 40 mg solution for injection in pre-filled syringe [1].

Other TNF- α inhibitors available on the Dutch market are etanercept (Enbrel[®]), infliximab (Remicade[®]), certolizumab pegol (Cimzia[®]) and Golimumab (Simponi[®]).

The SmPC of adalimumab mentions skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma) as a common (1-10 %) adverse drug reaction; melanoma occurs in 0.1-1 % of patients [1].

The current observation describes the association of adalimumab and neuroendocrine carcinoma of the skin, also known as Merkel cell carcinoma (MCC).

Merkel cell carcinoma is a skin cancer arising from Merkel cells, also known as neuroendocrine cells, in the lower part of the epidermis. Although the exact function of Merkel cells is unknown, they are thought to be touch receptors. MCC was first described in 1972 and only in the 1990s was the CK20 antibody developed to make it easily identified by pathologists. It is a relative rare carcinoma with an incidence 30 times less common than melanoma. Approximately 30% of MCC is fatal; the overall 5-year relative survival of first primary MCC is 62 %. It usually develops on sun-exposed skin as a rapidly growing painless, firm, flesh-colored to red or blue nodule. The differential diagnosis is broad, including benign and malignant tumors and miscellaneous cutaneous lesions. In most cases, due to its rarity, the diagnosis of MCC is often overlooked at initial presentation. Diagnosis is made by a skin biopsy to rule out other tumors or cysts. Factors strongly associated with the development of MCC are age over 65 years, fair skin, history of extensive sun exposure and chronic immune suppression (e.g. kidney or heart transplantation or HIV) [2-4]. In 2008 a Merkel cell polyomavirus (MCPyV) was detected to be frequently involved in MCC [5].

Reports

On November 3, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports concerning neuroendocrine carcinoma of the

skin associated with the use of adalimumab, reported by two different rheumatologists.

Information on the reported cases:

118478

This well documented serious spontaneous report from a rheumatologist concerned a female aged 71 years and older, with Merkel cell carcinoma on the lower leg following administration of adalimumab 40 mg once in two weeks and methotrexate 10 mg weekly for rheumatoid arthritis with a latency of 6 years after start of adalimumab and 7 years after start of methotrexate. Adalimumab and methotrexate were withdrawn. The patient was treated with surgery and radiotherapy twice. The patient recovered with sequel. Concomitant medications were calcium carbonate, pantoprazol, and risedronic acid. Patient had been known with a positive rheumatoid factor since 7 years.

122782

This well documented serious spontaneous report from a rheumatologist doctor concerned a female aged 51 – 60 years, with Merkel cell carcinoma following administration of adalimumab 40 mg once in two weeks and methotrexate 20 mg weekly for rheumatoid arthritis with a latency of 7 months after start of adalimumab and 1.5 year after methotrexate. The dose for methotrexate and adalimumab was not changed. Patient was surgically treated. The patient was recovering. Concomitant medication was hydroxychloroquine. Patient had been known with a positive rheumatoid factor since 2.5 years.

Other sources of information

SmPC

Merkel cell carcinoma is not mentioned in the SmPC of adalimumab (Humira®) [1]. Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), also known as non-melanoma skin cancer (NMSC) is described as a common (1-10 %) adverse drug reaction [1].

The SmPC of etanercept (Enbrel®), another TNF- α blocker specifically mentions Merkel cell carcinoma as adverse drug reaction observed in post-marketing experience with an unknown frequency [6].

In the SmPCs of other TNF- α blockers, infliximab (Remicade®) and golimumab (Simponi®) Merkel cell carcinoma is not described [7,8].

Literature

Merkel cell carcinoma was described once in association with adalimumab (search terms *adalimumab AND "Carcinoma, Merkel Cell"[Mesh]*) [9]. In this publication a patient was presented with a long-standing history of rheumatoid arthritis treated with adalimumab, methotrexate, and prednisone, who developed a painless, rapidly enlarging lesion that was found to be MCC with lymph node involvement. The author postulated that systemic immunosuppression may be a risk factor for the development of advanced-stage MCC. Treatment with the TNF-alpha inhibitor adalimumab may enhance this risk.

De Giorgi described the development of MCC after 18 months treatment with another TNF- α -blocker, etanercept in a 50 year old woman with psoriatic arthritis. The author provided several arguments for a cause-effect relationship: the relative young age, the rapid growth of the tumor in weeks' time, which was arrested after withdrawal of etanercept, which was replaced by corticosteroid and methotrexate [10].

Databases

On November 3, 2011, the database of the Netherlands Pharmacovigilance Centre contained two reports of neuroendocrine carcinoma of the skin in association with adalimumab. Because of this low number the Reporting Odds Ratio (ROR) could not be calculated.

On the 10th of January 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained only one case-report of a neuroendocrine carcinoma of the skin for another of the TNF- α -inhibitors, namely etanercept.

The WHO database of the Uppsala Monitoring Centre contained seven reports of neuroendocrine carcinoma of the skin in association with adalimumab with a ROR of 8.2 (95 % CI 3.8 -17.9). Two of these reports originated from the Netherlands, three from the USA, one from Spain and one from Italy. Reports were received between 2009 and 2011. Five of these were reported by physicians, for 2 of the reports the reporter was unknown. These reports concerned five women and one man. For three reports the age was not completed, the others concerned two adults (18-44 years, 45-65 years) and two elderly (65-74, > 75). The duration of use of adalimumab was between 7 months and 13 months in four patients and 3-6 years in the other patients. Three times methotrexate was also completed as suspected drug. Four patients used concomitant drugs: in two Dutch cases calcium carbonate/pantoprazole/risedronic acid and hydroxychloroquine were used, two other patients used prednisolone/acemetacin respectively mesalazine/rosiglitazone/simvastatin as concomitant medication). Five of the patients had recovered (without/with sequelae), one had not recovered and for one patient the course of the reaction was unknown.

On the 10th of January 2012 the database of the Uppsala Monitoring Centre of the WHO also contained several cases of neuroendocrine carcinoma of the skin in association with other TNF- α -inhibitors. See table 1.

Table 1. Reports of neuroendocrine carcinoma of the skin for the TNF- α -inhibitors in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
neuroendocrine carcinoma of the skin	Adalimumab	7	8.2 (3.8-17.9)
neuroendocrine carcinoma of the skin	Etanercept	14	31.2 (17.6-55.6)
neuroendocrine carcinoma of the skin	Infliximab	10	8.7 (4.5-16.8)
neuroendocrine carcinoma of the skin	Certolizumab pegol	1	-
neuroendocrine carcinoma of the skin	Golimumab	-	-

On November 23, 2011, the Eudravigilance database contained eight reports of neuroendocrine carcinoma of the skin in association with adalimumab, which was reported disproportionally (ROR = 11.6, 95% CI: 5.6 – 23.9). There was an almost complete overlap between these Eudravigilance- and WHO cases, except a case from France, in which an elderly patient with rheumatoid arthritis suffered from MCC on the left ankle 5 years after the start of adalimumab. As concomitant medication leflunomide had been used for 6 months in the past.

On the 10th of January 2012 the Eudravigilance database also contained several cases of a neuroendocrine carcinoma of the skin associated with the use of etanercept, infliximab, certolizumab pegol or golimumab. See table 2.

Table 2. Reports of neuroendocrine carcinoma of the skin for the TNF- α -inhibitors in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
neuroendocrine carcinoma of the skin	Adalimumab	8	11.6 (5.6-23.9)
neuroendocrine carcinoma of the skin	Etanercept	12	12.1 (6.6-22.2)
neuroendocrine carcinoma of the skin	Infliximab	18	10.8 (6.5-18.0)
neuroendocrine carcinoma of the skin	Certolizumab pegol	2	23.7 (5.8-96.1)
neuroendocrine carcinoma of the skin	Golimumab	0	-

Prescription data

The number of patients using adalimumab in the Netherlands is shown in table 3 [11].

Table 3. Number of patients using adalimumab in the Netherlands between 2006 and 2010

Drug	2006	2007	2008	2009	2010
adalimumab	4965	6691	9734	11935	14429

Mechanism

MCC is associated with a profoundly weakened immune system, such as in patients with HIV/AIDS, in patients who have received an organ transplant who are on medications that suppress the immune system, or people with chronic lymphocytic leukemia (CLL) and certain types of lymphoma [2]. Long-term suppression of the immune system (for many years), which suppresses cellular immune response, increases the risk of MCC. Severe immunosuppression appears to increase the risk of MCC more than that of malignant melanoma. In the post-transplant population the ratio of melanoma to MCC was 6:1 compared with about 65:1 in the general population [4].

After use of azathioprine fatal MCC was observed in three patients, who used concomitantly ciclosporin (two patients) or prednisone (one patient) [12]. It was suggested that Merkel cell carcinoma may be seen more commonly in immunosuppressed patients than in the normal population and that the oncogenic potential of azathioprine and ciclosporin should be borne in mind. Another publication described MCC after ciclosporine and antithymocyte globulin for aplastic anemia [13].

Tumor necrosis factor (TNF) might be involved in the development of MCC. Natural TNF has been reported to suppress the growth of human tumor cell lines to exert an antitumor effect, that is mediated by host immunity, and to have an antiangiogenic effect on tumor nutrient vessels. Intratumor injection of natural TNF was administered to a patient with recurrent MCC on the upper eyelid and to another patient with a large (2x2x1 cm) MCC on the cheek, who refused extensive surgical resection. Both patients showed complete remission within months [14]. In addition recombinant TNF has been reported to produce complete remission in another two cases of primary Merkel cell carcinoma. Another publication describes the direct intra-tumoral administration of tumor necrosis

factor over a period of 12 days in a 78-year-old woman with MCC in the mandibular area. Soon after the therapy ended, the lesion softened and decreased in size. After 1 month, only erythema was visible. The lesion had completely disappeared clinically and histologically after 5 months [15].

Class-effects

On the 10th of January 2012 the Lareb database contained only one case-report of a neuroendocrine carcinoma of the skin for another of the TNF- α -inhibitors, namely etanercept. In the WHO database this ADR has been reported for the aforementioned three drugs, 14, 10 and once respectively, all associations were reported disproportionately.

In the Eudravigilance database reports on this association were filed for etanercept, infliximab and cetolizumab pergol, and were reported 12,18 and 2 times respectively, also these associations were reported disproportionately. For this reason, a class effect cannot be excluded.

Discussion

Lareb has received two reports of neuroendocrine carcinoma of the skin in association with adalimumab.

In both patients also methotrexate (MTX) was reported as suspected drug. Among the seven cases of MCC in association with adalimumab in the WHO database, methotrexate was reported three times as a suspected drug as well. Methotrexate is an antineoplastic antimetabolite with immunosuppressant properties. For this reason a role of MTX in the development of MCC cannot be ruled out. However, MCC is not mentioned in the SmPC of methotrexate, nor did a literature search using the terms ("Methotrexate/adverse effects"[Mesh]) AND "Carcinoma, Merkel Cell"[Mesh] reveal any publications, although MTX has been on the market for more than thirty years.

In both patients in the Lareb database rheumatoid arthritis (RA) was the indication for use of adalimumab.

In several studies RA was associated with an increased risk of (not further specified) Non-Melanoma Skin Cancer (NMSC) [16]. Among RA patients, the development of NMSC was associated with use of prednisone and tumor necrosis factor (TNF) inhibitors alone or with concomitant methotrexate, whereas no association was found between use of methotrexate and development of NMSC.

Conclusion

Lareb has received two reports of neuroendocrine carcinoma of the skin in association with adalimumab. This association was supported by the WHO- and Eudravigilance data and one publication in the literature by Krishna [9]. Also for etanercept, another TNF- α -blocker, the association of MCC is described in the literature and was reported disproportionately in the WHO database; for etanercept MCC is mentioned in the SmPC. It is thought that immunosuppression in general, and TNF- α -blockade specifically could be a risk factor for developing Merkel Cell carcinoma, an aggressive skin cancer with high mortality rate, which is not easily recognized at initial presentation.

- Consider to mention neuroendocrine carcinoma of the skin in the SmPC of adalimumab.

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This signal has been raised on February 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

