

1.1. Lenalidomide and (aggravation of) psoriasis

Introduction

Lenalidomide (Revlimid[®]), was registered on the Dutch market in June 2007 and is indicated for *the treatment of multiple myeloma in combination with dexamethasone in patients who have received at least one prior therapy*. Lenalidomide is an immunomodulating drug with anti-neoplastic, anti-angiogenic, and pro-erythropoetic properties. Lenalidomide inhibits the proliferation of hematopoietic tumour cells, increases T-cell and Natural Killer (NK) cells immunity, and inhibits the production of pro-inflammatory cytokines (TNF-alpha and IL-6) [1].

Psoriasis is a chronic skin disease which manifests as erythematous papules and plaques covered with silver scales. There is a hyperproliferation of epidermal keratinocytes and inflammation of the epidermis and dermis [2]. Psoriasis is an immune-mediated disorder involving most predominantly, T-lymphocytes and dendritic cells. During the course of the disease, specific triggers tend to lead to exacerbations. These triggers include infections, psychological stress, and drugs (beta blockers, lithium, ACE-inhibitors, and NSAIDS) [3].

Thalidomide, which was re-introduced into the Dutch Market in 2008 has a similar pharmacological mechanism as lenalidomide and is also utilized for the treatment of multiple myeloma [4]. Literature reports have described exacerbation of psoriasis in patients treated with thalidomide but not yet with lenalidomide. The current observation discusses the association between lenalidomide and (aggravation of) psoriasis.

Reports

On November 17th, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained 2 reports on exacerbation of psoriasis in patients receiving treatment with lenalidomide.

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The first case, reported by a specialist doctor, concerns a male (patient A) aged 61-70 years who received treatment with lenalidomide 25mg (cyclical for 3-4 weeks), for multiple myeloma and after an unknown number of days developed an exacerbation of psoriasis. Although he was treated for the exacerbation by his general practitioner, the symptoms did not improve, and therefore, lenalidomide was withdrawn. The patient began to recover and the psoriasis skin lesions completely recovered with a latency of 42 days after withdrawal of lenalidomide. Concomitant medication consisted of oxycodone.

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Patient B, a male 71 years and older, was treated with lenalidomide 10 mg for chronic myeloid leukemia (off-label indication) and after a latency of 11 days his psoriasis aggravated. The patient was hospitalized and treated with topical steroids, the lenalidomide treatment was continued and the psoriasis was improving. The patient had a medical history of chronic myelomonocytic leukemia, hypertension, psoriasis, and had a coronary artery bypass graft. Concomitant medication consisted of, bumetanide, carbasalate calcium, buprenorphine, enalapril, lactulose, triamcinolone, clobetasol and desoximetasone.

Other Sources of Information

SmPC

The product information of lenalidomide describes several dermatological adverse drug reactions including rashes, eczema, dry skin, hyperhidrosis, hyperpigmentation and photosensitivity reactions. Psoriasis or an exacerbation of psoriasis is not mentioned as a potential ADR [1].

Literature

Two case reports from the literature describe exacerbation of psoriasis after treatment with thalidomide [5,6]. One report concerns a 46-year-old woman with Behcet's syndrome and orogenital ulceration, who had stable chronic plaque psoriasis of the elbows, which was untreated and she experienced no exacerbations (flares) in a period of 5 years. She was treated with thalidomide and within 4 days there was an aggravation of her psoriasis. Treatment with thalidomide was stopped, the patient was treated with methotrexate, and after 3 months she recovered [6].

Another report concerns a 41-year-old woman with oral ulcers and blisters which was histologically confirmed to be erythema multiforme. She also had psoriasis with occasional flare-ups. She was treated with dapson for 2 years but this did not result in much improvement, thus she was then treated with thalidomide. Two weeks after start, the psoriasis aggravated intensely. Thalidomide was suspected to have been the cause of the psoriasis flares and was therefore withdrawn. The patient was treated and she recovered after 2 weeks [5].

Den, A, *et.al.* describe one patient who received treatment with lenalidomide and developed an interstitial granulomatous dermatitis which clinically manifested itself as erythematous annular plaques [7]. This may have some resemblance to how psoriasis, a complex immune-mediated disease, may develop.

To the best of our knowledge, there are no other publications on psoriasis, or on an exacerbation of psoriasis in association with lenalidomide.

Databases

On November 17th, 2011, the Lareb database contained 2 reports on exacerbation of psoriasis in patients receiving treatment with lenalidomide. Due to the limited number of reports, the reporting odds ratio (ROR) was not calculated. On the 10th of January 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained no cases of psoriasis for thalidomide.

On November 17th, 2011, the WHO database of the Uppsala Monitoring Centre contained 2 reports of psoriasis aggravated (Lareb reports included) in association with lenalidomide and 2 reports of psoriasis in association with lenalidomide, the combined ROR for the 4 reports is 0.1, (95% CI 0.1-0.3), which is not disproportional.

On the 10th of January 2012 the database of the Uppsala Monitoring Centre of the WHO contained 9 cases of psoriasis associated with thalidomide. See table 1.

Table 1. Reports of psoriasis for lenalidomide and thalidomide in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Psoriasis (aggravated)	Lenalidomide	4	0.1 (0.1-0.3)
Psoriasis	Thalidomide	9	0.2 (0.1-0.4)

On November 24th, 2011, the Eudravigilance database contained only two reports of psoriasis in association with lenalidomide. These cases originate from the Netherlands.

On the 10th of January 2012 the Eudravigilance database contained 4 cases of psoriasis associated with the use of thalidomide. See table 2.

Table 2. Reports of psoriasis for lenalidomide and thalidomide in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Psoriasis	Lenalidomide	2	-
Psoriasis	Thalidomide	4	0.3 (0.1-1.9)

Prescription Data

The number of patients using lenalidomide, an orphan drug, in the Netherlands is shown in table 1.

Table 1. Number of patients using lenalidomide in the Netherlands between 2007 and 2010 [8]

Drug	2007	2008	2009	2010
lenalidomide	75	452	671	855

Mechanism

The pharmacological mechanism of how lenalidomide triggers an exacerbation of psoriasis has yet to be described. Lenalidomide, a second generation immunomodulatory compound (IMiD), is a derivative of thalidomide, created by adding an amino group to the 4th carbon of the phthaloyl ring, and by removing a carbonyl group [9]. Thalidomide and lenalidomide are analogue drugs exhibiting a similar pharmacological mechanism of action. They both are immunomodulating drugs and TNF-alpha inhibitors [1,4]. Lenalidomide also has direct apoptotic effects on cancer cells and is a more potent TNF-alpha inhibitor than thalidomide [4,9]. However, the exact mechanism of action of lenalidomide remains unclear [9].

The inflammatory cytokine, TNF-alpha regulates immune and inflammatory responses to infection and plays an important role in diseases such as psoriasis and rheumatoid arthritis. Thalidomide inhibits TNF-alpha production in vitro and in vivo in a dose-dependent manner [5,6]. Thalidomide modifies T-cell function by decreasing the CD4/CD8 ratio [6]. Reports have shown that thalidomide has both inhibitory and enhancing effects on TNF-alpha production. One report describes an open trial of 35 patients with different skin diseases receiving treatment with thalidomide in which for 2 patients with psoriasis this treatment was ineffective [6]. Dobson, C, *et. Al.* conclude that thalidomide has a “bidirectional effect” on TNF-alpha and propose that thalidomide increases TNF-alpha within psoriatic skin lesions, leading to an exacerbation. Thalidomide and analogue drugs have stimulatory and inhibitory effects by co-stimulating CD4 and CD8 T-cells [5]. However, the conditions which determine the inhibition or stimulation of TNF-alpha are unknown. Dobson, C, *et. Al.* hypothesize that thalidomide stimulates TNF-alpha in psoriatic patients but due to polymorphisms in the TNF-alpha gene, the exacerbations may be less in some patients [6]. It is likely that lenalidomide has a similar mechanism leading to TNF-alpha stimulation and exacerbation of psoriasis.

Class-effects

Lenalidomide belongs to the class of 'Immunomodulators'. The other drug available on the Dutch market as an orphan drug, is thalidomide. On the 10th of January 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained no cases of psoriasis for thalidomide. The database of the Uppsala Monitoring Centre of the WHO contained cases on thalidomide and psoriasis, the Eudravigilance database contained 4 cases of psoriasis associated with the use of thalidomide, but is not reported disproportionately. However, the use of both drugs is limited, so a class effect cannot be excluded.

Discussion and Conclusion

Lareb has received only two cases of exacerbation of psoriasis following the administration of lenalidomide, however, they are strong cases. In one case (A) there was a positive dechallenge. In the other case (B) the psoriasis exacerbation was treated and lenalidomide was not discontinued and the exacerbation abated, but the dose was lower in this case (10mg versus 25mg). In the second case, the patient had enalapril as a concomitant medication, which may be a confounding factor as that this drug is also a known cause of psoriasis [3].

The association between exacerbation of psoriasis and lenalidomide in the WHO database is not disproportional. There are two well documented case reports in the literature [5,6] describing thalidomide and exacerbation of psoriasis and the possible mechanism involved. Lenalidomide most probably has an analogous mechanism leading to an exacerbation of psoriasis.

Lenalidomide is an effective treatment for patients with multiple myeloma, however, in patients who also have psoriasis, a causal relationship of lenalidomide and exacerbation of psoriasis is plausible and this association is a possible new signal.

- Possible new signal of lenalidomide associated with (aggravation) of psoriasis

References

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20-04-2012: This signal was sent to the Marketing Authorization Holder (MAH) of lenalidomide after review by the Medicines Evaluation Board. The MAH remarked that it is more accurate to refer to lenalidomide as 'structurally related' to thalidomide, instead of mentioning it as a 'derivative'. The mechanism of action is different for both drugs: lenalidomide is tumoricidal and immunomodulating and thalidomide is anti-angiogenic.

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).