REVIEW

Cutaneous adverse reactions to lenalidomide

S. Imbesi a,∗, A. Allegra b, G. Calapai c, C. Musolino b, S. Gangemi a,d

a Department of Clinical and Experimental Medicine, School and Unit of Allergy and Clinical Immunology, University of Messina, Italy
b Division of Hematology, University of Messina, Italy
c Department of Clinical and Experimental Medicine and Pharmacology, Section of Pharmacology, University of Messina, Italy
d Institute of Biomedicine and Molecular Immunology “A. Monroy” (IBIM) – Consiglio Nazionale delle Ricerche (CNR), Palermo, Italy

Received 14 May 2013; accepted 8 July 2013
Available online 25 October 2013

KEYWORDS
Lenalidomide; Immunomodulatory drugs; Multiple myeloma; Myelodysplastic syndromes; Amyloidosis; Adverse cutaneous reactions; Stevens–Johnson syndrome; Erythema multiforme; Toxic epidermal necrolysis

Abstract Lenalidomide is an immunomodulatory drug (IMiD) used principally in the treatment of multiple myeloma (MM), myelodysplastic syndromes (MS) and amyloidosis. Adverse reactions related to lenalidomide include myelosuppression (mainly neutropenia but also thrombocytopenia), gastrointestinal problems, skin eruption, atrial fibrillation and asthenia, decreased peripheral blood stem cell yield during stem cell collection, venous thromboembolism, and secondary malignances. In this review we focused our attention on the cutaneous adverse reactions to lenalidomide.

© 2013 SEICAP. Published by Elsevier España, S.L.U. All rights reserved.

Introduction

Lenalidomide is an immunomodulatory drug (IMiD) used principally in the treatment of multiple myeloma (MM), myelodysplastic syndromes (MS) and amyloidosis. Furthermore, several studies on the association between lenalidomide and the standard therapies are ongoing in patients affected by diffuse large B-cell lymphoma.1 However, lenalidomide is the most potent analogue of thalidomide but causes fewer adverse reactions, thus showing a better safety profile.

These drugs have direct antitumour action and indirect immunomodulatory and anti-angiogenic effects. In
fact, through induction of cell cycle arrest and caspase-
dependent apoptosis they may kill myeloma multiple cells. 
Moreover some authors have shown that they also target a 
stem cell-like subpopulation.  

More specifically, IMiDs directly induce apoptosis of MM 
cells via caspase-8 activation, block MM cell–bone marrow 
stromal cell interactions, inhibit secretion of cytokines in 
the bone marrow responsible for MM cell growth and sur-
vival, and inhibit angiogenesis.  

Moreover, IMiDs increase NK cell cytotoxicity against MM 
cells, induce T-cell proliferation, modulate IL-12 produc-
tion and interfere with the action of several cytokines, 
such as IL-2, IFN-γ, IL-1β, IL-6, GM-CSF, and TNF- 

Adverse reactions related to lenalidomide include 
myelosuppression (mainly neutropenia but also thrombo-
cytopenia), gastrointestinal problems, skin eruption, atrial 
fibrillation, asthenia, and decreased peripheral blood stem 
cell yield during stem cell collection when lenalidomide is 
used after a long period of time. 

In addition, when lenalidomide is combined with dexam-
ethasone or other conventional cytotoxic agents, there is 
an increase in the incidence of venous thromboem-
bolic events. The venous thromboembolic risk with 
lenalidomide–dexamethasone is further increased with 
concomitant erythropoietin. 

Finally, there is an increased incidence of secondary 
malignancies in newly diagnosed MM patients receiving 
lenalidomide plus melphalan/prednisone. 

Literature review 

Known complications of cutaneous areas are due to lenalido-
mide side effects.

A retrospective study found incidences of skin eruptions, 
generally mild, in 43% of 23 patients with MM treated with 
lenalidomide and dexamethasone and in 29% of seven with 
MM on lenalidomide alone. 
The skin eruptions were of morbilliform, urticarial, 
dermatitic, acniform, and undefined forms. Severe skin 
eruptions required permanent discontinuation of lenalido-
mide therapy in two patients. In 23 patients (72%), skin 
eruptions occurred in the first month after therapy was 
initiated while delayed-onset skin eruptions occurred in nine 
(28%). 

Celgene Corporation has received 12 reports of 
Stevens–Johnson Syndrome (SJS), three reports of Erythema 
multiforme (EM) and one report of toxic epidermal necroly-
sis (TEN) among approximately 57,000 patients who received 
lenalidomide from its launch on the market on December 
27, 2005 through to June 26, 2008. Ten SJS cases were 
spontaneous reports from US health care professionals while 
the other two cases were reported by the US investigator-
initiated trials. The 12 cases occurred in seven women and 
five men with a median age of 63.5 years (range, 50–83 years). 

Erythema multiforme occurred in three patients (two 
women and one man, aged 85, 74, and 70 years, respec-
tively) after 7, 24 and 112 days from the start of the 
treatment with lenalidomide in association with dexameth-
asone. Cutaneous lesions were accompanied by blistering,

sores, mucosal involvement, crusting, and fever. Two 
patients were hospitalised, and one died. 

Toxic epidermal necrolysis was reported in an 85-year-
old woman hospitalised 18 days after initiating lenalidomide 
with dexamethasone for multiple myeloma. 

Stevens–Johnson Syndrome was described in a patient 
with multiple myeloma who received lenalidomide in com-
bination with prednisolone. In literature, there are various 
reports as to the correlation between SJS and lenalidomide 
treatment. Among these cases, one was particularly 
interesting because the patient experienced a complete 
remission of the multiple myeloma after the severe 
cutaneous reaction. A 69-year-old woman with multiple 
myeloma presented erythema, mucocutaneous tenderness 
and haemorrhagic lesions which developed into a SJS at the 
end of the first cycle of lenalidomide and prednisolone com-
bination treatment regimen. Subsequently, lenalidomide 
treatment was stopped and replaced with dexamethasone 
and clodronate. Upon patient follow-up, serum and urine 
were negative for M protein as was immunofixation and <5% 
plasma cells in bone marrow were found; thus complete 
remission was achieved. 

It may be that the cytokine storm caused by SJS could 
have determined the induction of idiotype-specific T cells 
able to act against the myeloma cells. 

Another case of SJS was described in a 51-year-old man 
fected by primary plasma cell leukaemia and treated 
with lenalidomide and dexamethasone. 

Borouah instead described the onset of a severe cutaneous manifestation 
probably induced by lenalidomide in a 73-year-old Caucasian 
female undergoing induction therapy for multiple myeloma. 
In this case lenalidomide was substituted with bortezomib 
for her induction therapy and the patient did not experience any further cutaneous reactions. 

In most cases the therapy with lenalidomide is not com-
pletely discontinued but only temporarily interrupted or 
reduced in dosage. 

An interesting study was conducted to evaluate the his-
tocompatibility antigen genes, HLA-A, B, C, DRB1 and DQB1, 
of Italian MM patients with dermatologic adverse reactions 
after lenalidomide treatment. 

Seven women and three men (mean age 68 ± 10.81 
years) were included in two different controlled trials. They 
were randomised to receive lenalidomide-prednisolone or 
lenalidomide-dexamethasone with a specific treatment 
scheme. 

Three patients experienced dermatologic complications: 
urticaria, EM and SJS. The polymerase chain reaction (PCR) 
amplification followed by sequence specific primers (SSP) 
HLA typing was performed and the analysis of the Italian 
patients showed that the two severe dermatologic 
complications were both related to HLA-DRB1*1501 and 
HLA-DQB1*0602, whereas the patient with urticaria pre-
sented HLA-DRB1*1502 and HLA DQB1*0601. The authors 
concluded that application of HLA-genotyping as a screening 
tool before prescribing lenalidomide could contribute 
in evaluating the risk factors and preventing severe 
lenalidomide-induced dermatologic reactions. 

A particularly rare manifestation was described in a 
60-year-old patient who received lenalidomide for the treat-
ment of a plasmacytoma. After four months of treatment, 
red papules appeared on the extremities and the trunk
following the lines of Blaschko. The lesions nearly disappeared during drug-free intervals and appeared with renewed intensity after readministration of a therapy cycle.\textsuperscript{21}

Another manifestation described regards a patient treated with lenalidomide again for multiple myeloma with the appearance of erythematous annular plaques on the trunk and extremities. Skin biopsy specimens revealed diffuse interstitial granulomatous infiltrates of lymphocytes, histiocytes, eosinophils and palisading degenerated collagen.\textsuperscript{22}

Finally, a purpuric drug eruption was reported in a 74-year-old man receiving lenalidomide and dexamethasone therapy after having been erroneously diagnosed with MM. The patient interrupted both medications within one week from administration due to oedema, fatigue, dizziness, gastritis, and a mildly pruritic truncal rash, thus obtaining quick resolution of symptomatology. Subsequently, after the correct diagnosis of amyloidosis, he restarted treatment with lenalidomide, dexamethasone and melphalan thus developing intermittently pruritic eruption on his chest, lower abdomen, and extremities within a week which however spared mucosa and conjunctivae. The eruption consisted of polycyclic erythematous thin plaques with dusky centres bearing scant scale and erythematous, no blanching macules.\textsuperscript{23}

Conclusions

Dermatological side effects are a known complication due to lenalidomide use with a frequency ranging from 12% to 43%, with the highest rates similar to those due to thalidomide use. Most eruptions occur during the first month of therapy and have been described as morbilliform, urticarial, dermatitic, acneliform, or undefined.\textsuperscript{24} Physicians prescribing lenalidomide should monitor their patients for possible cutaneous adverse reactions, in particular if patients have a history of thalidomide skin eruption.

Due to the increasing number of prescriptions of lenalidomide for the treatment of myeloma multiple and other similar haematological conditions, the potential ability of lenalidomide to induce severe cutaneous adverse reactions must be taken into consideration.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Patients’ data protection. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflict of interest to declare.

Acknowledgements

The authors would like to thank Ms. Antonina Donato for the editing of the manuscript.

References