

A Tailored 7- to 10-Day Lenalidomide Desensitization Protocol

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J Investig Allergol Clin Immunol 2024; Vol. 34(1): 49-50
doi: 10.18176/jiaci.0914

Key words: Desensitization protocol. Lenalidomide. Drug-induced hypersensitivity syndrome.

Palabras clave: Protocolo de desensibilización. Lenalidomida. Síndrome de hipersensibilidad inducido por fármacos.

The oral immunomodulatory drug lenalidomide is a synthetic derivative of thalidomide used in combination with dexamethasone to treat patients with multiple myeloma [1]. It acts by inducing apoptosis of tumor cells and stimulating the host immune response through the activation of cytotoxic T lymphocytes and natural killer cells [2,3]. Cutaneous adverse effects are a known complication of lenalidomide, with a prevalence ranging from 6% to 43% [4].

Nonimmediate drug hypersensitivity reactions (DHRs) are believed to be mediated by T cells. The most common clinical presentations are maculopapular rash and delayed urticaria. When no alternative agent is available and the use of the culprit drug is mandatory, drug desensitization becomes the sole choice for management [5]. However, there is little experience with delayed DHRs involving chemotherapeutic agents [6].

Few data have been published on desensitization with lenalidomide. Previously proposed protocols are long (lasting between 16 days and 7 months), complicated, and, sometimes, clinically inapplicable [7-9]. Our group previously reported a case of desensitization to lenalidomide based on a shorter and more effective protocol [1].

We present a retrospective observational study based on clinical practice at La Paz University Hospital in Madrid, Spain. We included patients with multiple myeloma treated

with lenalidomide in 21-day cycles between 2018 and 2022. All patients developed nonimmediate DHRs and underwent a desensitization protocol.

We included 7 patients (4 women). The median age was 68 years (range, 56-80 years). Treatment was administered at 10 mg daily in 4 patients and 25 mg daily in 3. Cycles were prescribed for 21 days, with a 7-day interval between cycles.

All patients developed mild nonimmediate skin reactions during treatment with lenalidomide. Three had associated eosinophilia, and 1 of these presented mildly elevated transaminases. The median time to cutaneous symptoms was 8 days between cycles 1 and 10. In 4 patients, the skin lesions took more than 15 days to resolve. Two patients underwent a lymphocyte transformation test, which yielded a positive result.

Based on allopurinol desensitization protocols for nonimmediate reactions [10], we designed a 7-day protocol to reach the dose of 10 mg and a 10-day protocol for 25 mg (Table). The starting dose was 0.1 mg in a dilution of 1/100 of the target 10 mg, escalating gradually. Of the 7 patients, 4 presented adverse reactions during desensitization. All reactions were mild (eg, erythema and intense itching). The symptoms developed during the first desensitization cycle with 5 mg (in 1 patient) and 7.5 mg (in 3 patients). We prescribed antihistamines (or topical corticosteroids) for these reactions, and the last tolerated dose was maintained before increasing to the next after symptoms had resolved.

Once the target dose was tolerated, the modified tailored protocol was maintained in the following cycles. All patients tolerated their target dose. Since severe itching is a common adverse effect of lenalidomide, we premedicated every patient with antihistamines after the first cases, and no further reactions occurred. All patients tolerated their target dose (10 mg in 4 and 25 mg in 3). One patient has been receiving

Table. Lenalidomide Desensitization Protocol for Target Doses of 10 and 25 mg

Day	Dilution	Dose	Day	Dilution	Dose
1	1/100	0.1 mg	1	0.4/100	0.1 mg
2	5/100	0.5 mg	2	2/100	0.5 mg
3	10/100	1 mg	3	4/100	1 mg
4	25/100	2.5 mg	4	10/100	2.5 mg
5	50/100	5 mg	5	20/100	5 mg
6	75/100	7.5 mg	6	30/100	7.5 mg
7	100/100	10 mg	7	40/100	10 mg
			8	60/100	15 mg
			9	80/100	20 mg
			10	100/100	25 mg

premedication continuously, with the result that she received only 1 desensitization cycle. She is currently taking 10 mg/d. The remaining 6 patients receive lenalidomide in 21-day cycles, with an interval of 1 week between cycles. Of these 6 patients, 2 are currently undergoing desensitization (one has completed 14 cycles and the other 22), 2 died during treatment (for reasons unrelated to desensitization), and 2 discontinued owing to gastrointestinal toxicity. None of the patients stopped desensitization owing to failure of the procedure.

The 2 patients currently undergoing desensitization attend the day hospital once per month. They receive the first dose under surveillance, and the rest are taken by the patient at home. They also receive ebastine 20 mg concomitantly.

Very little experience and few protocols have been reported for desensitization to lenalidomide [7-9,11]. One case series in Japan reported 5 patients who successfully completed their desensitization protocol. All of them tolerated the target dose without adverse reactions. The protocol started with a dose of 2.5 mg given 1 day a week and then slowly increased the dose every cycle, reaching the full dose of 10 mg in approximately 4 months and 25 mg in 7 months [8]. In Turkey, Demir et al [11] performed a 16-day desensitization protocol in 10 patients who had experienced nonimmediate hypersensitivity reactions. The protocol was performed with an initial dose of 1/100 of the target dose, giving 2 different doses each day, at 09:00 and 15:00 [11].

We created a simple, fast, and tailored desensitization protocol that is easily applied in patients with multiple myeloma. It has proven to be safe and effective since we reported the first case of desensitization in 2020 [1].

Desensitization appears to be a safe option in patients who experience DHRs and who need to continue treatment. While adverse reactions can occur, these are often mild. Adverse reactions can be reduced by adapting the protocol according to the dose required and the patient's response. In this way, tolerance to lenalidomide can be achieved, enabling continuation of treatment, which has a significant impact on patient quality of life and prognosis.

The allergology study is challenging because of the short time available to perform the skin tests, concomitant corticosteroid treatment, and the lack of validation of skin tests for DHRs to the drug [6]. The lymphocyte transformation test can be useful as an *in vitro* diagnostic tool [1] for demonstrating the underlying mechanism.

In conclusion, to our knowledge, this is the simplest, shortest, and most effective lenalidomide desensitization protocol. It enables treatment to be restarted sooner and the therapeutic dose to be reached faster, with very low risks and a positive impact on quality of life and prognosis. The desensitization protocol we used is tailored and, as such, can be lengthened or shortened depending on the patient's tolerance.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

Our experience with this desensitization protocol was presented as an oral communication at the SEAIC INTERNATIONAL SYMPOSIUM 2022 (award for best oral communication).

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■ Manuscript received January 24, 2023; accepted for publication May 16, 2023.

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