

Tolerance Induction to Antituberculosis Drugs in a Patient With Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis Overlap

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Abstract

Tolerance induction and desensitization in Stevens–Johnson syndrome (SJS) or in toxic epidermal necrolysis (TEN) have been described as an absolute contraindication by some authors, but there are cases where there is no treatment alternative. Tuberculosis (TB) remains a leading cause of morbidity and mortality in developing countries and ranks alongside HIV as a leading cause of death worldwide. Severe drug reactions, such as SJS and TEN, occurring in these individuals are life-threatening. Since alternative therapies for TB are limited, the role of desensitization and reintroduction becomes essential. We describe a case of tolerance induction to anti-TB drugs in a patient with SJS/TEN overlap syndrome using a specifically designed premedication, comedication, and desensitization protocol.

Keywords

tolerance induction, Stevens–Johnson syndrome, toxic epidermal necrolysis, isoniazid, rifampin, comedication

An adverse drug reaction is defined by the World Health Organization as a harmful and undesirable response to a drug that is produced at a dose normally used in humans.¹ Adverse drug reactions affect about 10% to 20% of hospitalized patients. Severe reactions, such as anaphylaxis, Stevens–Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), are associated with high morbidity and mortality. Prevention of these reactions when there is no alternative treatment is through desensitization. The term desensitization is defined as the induction of lack of immune response (hypersensitivity reaction) to a specific antigen.²

In contrast to desensitization by specific immunotherapy with common allergenic peptides (allergens and insect venoms), drug desensitization only provides a temporary state of tolerance, being present as long as the drug remains in the circulation (3–4 half-lives). After treatment discontinuation, drug hypersensitivity

may occur in a short time, and new drug desensitization process will be required.^{2,3}

From the first case of desensitization to a drug developed by Peck, many investigations have addressed the pathophysiology of drug desensitization.⁴ Although the mechanisms remain poorly understood, desensitization has been used to induce immunological tolerance in patients who have non-IgE-mediated or IgE-mediated reactions.⁵ Type I IgE-mediated reactions involve mast cell activation which is a result of the antigenic cross-linking between FcεRI receptors and IgE ligands

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allowing the degranulation and release of their immunological mediators. *In vivo* and *in vitro* mice models of rapid mast cell/IgE desensitization have provided evidence that increasing doses of the antigen administered at fixed time intervals induce highly specific and prolonged hyporeactivity at the desensitized antigen-triggering doses.⁵

Desensitized mast cells do not release a significant amount of interleukin-6 or tumor necrosis factor- α , indicating a lack of late phase mast cell activation, which is considered to be mechanistically related to the success of the desensitization protocol.⁶

Desensitization in type II and type III hypersensitivity reactions is contraindicated, presumably because the interaction of antigen and antibody leading to the activation and consumption of complement in these reactions is not amenable to desensitization.⁷

Desensitization in type IV hypersensitivity reactions is used less frequently than in type I reactions, and there have been only few reports on the mechanism of this type of desensitization.¹² Late hypersensitivity reactions to drugs can be caused by different mechanisms. The specific involvement of T lymphocytes is suggested by a positive response in late readings of intracutaneous tests and/or patch tests. The cytotoxic functions of CD4 or CD8 lymphocytes are predominant in type IVc reactions. Some studies have shown that the number of CD25+ CD4+ T cells increases significantly after desensitization, and the number of CD8+ cells decreased from 94% to 35% during desensitization, suggesting that CD4+ and CD25+ regulatory T cells may have a suppressive effect on the effector function of CD8+ T lymphocytes.⁷

Case Report

A 6-year-old male patient presented with the following history: his 9-year-old sister died due to SJS secondary to anti tuberculosis (TB) drugs used to treat miliary TB. The patient had a diagnosis of lymph node TB



Figure 1: Rash Maculopapular with target lesions, with blistered lesions sloughing of necrotic skin.

determined in October 2015 by lymph node biopsy. He began treatment with isoniazid and rifampin and presented 15 days later with an adverse reaction consisting of erythematous dermal lesions that evolved to blistered lesions affecting 28% of the skin surface, including oral mucosa and a positive Nicholsky sign, being categorized as SJS/TEN overlap (skin detachment levels of 10% to 29% of the body surface area) (Figure 1). He required hospitalization in the intensive care unit and received systemic corticosteroids, intensive fluid therapy, and assessment and management by our Allergy and Clinical Immunology Department.

An associated immunodeficiency was ruled out (negative or normal ELISA test for HIV, immunoglobulins, blood count, cultures and polymerase chain reaction (PCR) for *Cytomegalovirus*), sensitization to isoniazid and rifampin was demonstrated through patch tests with the contraindication for oral challenge. Given the need to treat lymph node TB and the lack of acceptable alternatives. In a Clinical Review Committee at our department, benefits and risks were assessed, concluding a need to initiate an individualized tolerance induction protocol that offered the greatest possible safety for the patient.

Taking into account the type of adverse reaction presented, the family history of allergy to anti-TB drugs, and the need for treatment, the patient was classified as a high-risk patient, so it was decided to initiate tolerance induction to isoniazid and rifampin with a slow oral desensitization scheme accompanied by premedication and comedication (Tables 1 and 2). This protocol was begun 4 weeks after hospital discharge, which was 6 weeks after the onset of symptoms. Surveillance during the protocol was made by peak flow measurement, pulse oximetry, vital signs every 15 min with rescue medications available, the follow-up was made with complete

Table 1. Rifampin and Isoniazid Dilutions Prepared for Induction Tolerance Protocol.

Solutions	Volume	Dilution	Concentration
Rifampin (20 mg/ml) suspension			
Solution A	15 ml	1/10,000	.002 mg
Solution B	15 ml	1/1,000	.02 mg
Solution C	15 ml	1/100	.2 mg
Solution D	15 ml	1/10	2 mg
Solution E	15 ml	Matrix	20 mg
Isoniazid (100 mg) tablets			
Solution A	15 ml	1/100,000	.001
Solution B	15 ml	1/10,000	01
Solution C	15 ml	1/1,000	.1
Solution D	15 ml	1/100	1
Solution E	15 ml	1/10	10
		Tablets	100 mg

Table 2. Slow Oral Tolerance Induction With Premedication and Comedication Protocol for Isoniazid and Rifampin.

Premedication	Since day 1 to day 3			
	<ul style="list-style-type: none"> • Prednisone 20 mg (.75 mg/kg day) • One tablet taken 1 time a day for 28 days at 08:00. • Loratadin 5 mg/5 mL syrup • 5 mL taken 1 time a day during anti-tuberculosis treatment (6 months) • Montelukast 5 mg • One chewable tablet taken 1 time a day during antituberculosis treatment (6 months) • Ranitidine 150 mg (2–6 mg/kg/day) • One tablet taken 2 times a day during anti-tuberculosis treatment (6 months) 			
Tolerance induction	Day	Steps	Accumulated dose	
Rifampicin: scale to treatment 10–20 mg/kg/day	3: Three hours regime: double dose every 30 min Six steps by day	Solution A 1. .002 mg (1 mL) 2. .004 mg (2 mL) 3. .008 mg (4 mL) 4. .016 mg (8 mL)	Hour 08:00 08:30 09:00 09:30	.15 mg/day
Dose maintenance: 300 mg/day		Solution B 5. .040 mg (2 mL) 6. .080 mg (4 mL)	10:00 10:30	
Start 3 days after premedication				
Initial dose: 1/1000: mild reactions 1/10 000: moderate reactions 1/100 000: severe reactions	4: Three hours regime: double dose every 30 min Six steps by day	7. 12 mg (6 mL) Solution C 8. .2 mg (1 mL) 9. .4 mg (2 mL) 10. .8 mg (4 mL) 11. 1.6 mg (8 mL)	08:00 08:30 09:00 09:30 10:00 10:30	5.12 mg/day
		Solution D 12. 2 mg (1 mL)		
	5: Three hours regime: double dose every 30 min Six steps by day	13. 4 mg (2 mL) 14. 8 mg (4 mL) 15. 16 mg (8 mL)	08:00 08:30 09:00 09:30	308 mg/day
		Solution E 1. 40 mg (2 mL) 2. 80 mg (4 mL) 3. 160 mg (8 mL)	10:00 10:30	
	6: Dose maintenance	1. 300 mg/day (tablets)	300 mg/day	
Isoniazid: scale treatment up to 10–20 mg/kg/day	6: Three hours regime: double dose every 30 min Six steps by day	Solution A 1. .001 mg (1 mL) 2. .002 mg (2 mL) 3. .004 mg (4 mL) 4. .008 mg (8 mL)	08:00 08:30 09:00 09:30 10:00	.71 mg/day
Dose maintenance: 200 mg/day		Solution B 5. .02 mg (2 mL) 6. .04 mg (4 mL)	10:30	
Start 3 days after start rifampicine				
Initial dose: 1/1000: mild reactions	7: Three hours regime: double dose every 30 min Six steps by day	1. .08 mg (8 mL) Solution C 2. .2 mg (2 mL) 3. .4 mg (4 mL)	08:00 08:30 09:00 09:30	7.48 mg/day

(continued)

Table 2. Continued

Premedication	Since day 1 to day 3			
I/10 000: moderate reactions		4. .8 mg (8 mL)	10:00	
I/100 000: severe reactions		Solution D	10:30	
		5. 2 mg (2 mL)		
		6. 4 mg (4 mL)		
	8: Two hours regime: double dose every 30 min	1. 8 mg (8 mL)	08:00	148 mg/day
	Six steps by day	Solution E	08:30	
		2. 20 mg (2 mL)	09:00	
		3. 40 mg (4 mL)	09:30	
		4. 80 mg (8 mL)		
	9: Dose maintenance	1. 200 mg/day (2 tablets)		100 mg/day
Since day 10	Full dose of rifampicin (300 mg/day) Full dose of isoniazid (200 mg/day) Add pyrazinamide and ethambutol And continue treatment in an ambulant form			

blood count, liver function tests, and urinalysis on admission, at 6 weeks, at 3 months, and at 6 months. He had no reactions during the tolerance induction period. He manifested no clinical adverse reactions during this year of treatment.

Discussion

Hypersensitivity reactions to anti-TB drugs have been reported in 4% to 5% of the general population, presenting adverse drug reactions ranging from maculopapular or urticarial rash to severe reactions (such as anaphylactic shock, SJS, and TEN.). The presentation of SJS secondary to anti-TB drugs is a rare manifestation and occurs only in 0.96% of cases.⁸

However, it should be noted that skin tests in delayed drug hypersensitivity often have a low sensitivity and specificity¹⁷ and are therefore in any case not a very reliable predictive diagnostic tool.

The diagnosis of delayed hypersensitivity reactions offers a diagnosis challenge, since most patients have taken several medications before the incident, the relationship between the drug adverse reaction and a single drug is difficult to establish. Initially, all drugs should be discontinued, and in a period of not less than 2 weeks, the existence of a sensitization should be demonstrated. Rechallenge with the suspected drug could be considered the “gold standard,” but carrying the risk of a more severe reaction is contraindicated in severe reactions. *In vitro* tests lack sensitivity compared to clinical history and/or skin tests and have not been well validated, so its use in clinical practice is limited. Patch tests are used in specialized centers for the diagnosis of delayed

hypersensitivity drug reaction but has to be noted that skin tests in delayed drug hypersensitivity often have a low sensitivity and are therefore in any case not a very reliable predictive diagnostic tool.^{9,10}

Nonimmediate adverse reactions are much more frequent than immediate reactions with anti-TB drugs. Genetic polymorphisms in the enzymes responsible for anti-TB drugs metabolism such as CYP2C19, CYP2C9 and HLAB12 are associated with the development of hypersensitivity reactions such as Erythema multiforme and SJS.¹¹

Desensitization in SJS or in TEN has been described as an absolute contraindication by some authors,⁷ but in more recent times, cases of desensitization in severe reactions have been reported: Minor in 2012 with a successful desensitization protocol in a SJS to veramufanib,¹² Witcher in 2018 with a successful desensitization in a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome to phenobarbital, Thong in 2014 with a successful desensitization rechallenge for anti-TB drug allergy in 2 patients with SJS, and Siripassorn in 2018 with a success rate of 62% of drug desensitization in patients with severe allergic reactions demonstrating the myth of not being able to desensitize or induce tolerance in severe adverse reactions like SJS, TEN, DRESS syndrome, and others hypersensitivity syndromes.^{12–15}

However, given the need for anti-TB treatment and the absence of first-line treatment alternatives in this patient, it was necessary to propose a new tolerance induction scheme for rifampin and isoniazid.^{16–18}

Selection of the specific desensitization or tolerance induction protocol will depend on the patient's

conditions, the presence of atopy, comorbidities, and the type of adverse reaction presented.^{7,19}

There is no consensus on the value of premedication or comedication during desensitization. Considering that the adverse reactions associated with anti-TB drugs are frequently delayed reactions, we chose systemic corticosteroids, antihistamines (H1 and H2), and antileukotrienes for premedication and comedication.^{7,19,20}

In conclusion, the slow tolerance induction scheme for anti-TB drugs in a patient who had presented with SJS/TEN overlap after receiving those drugs was effective using the described protocol and with continuous hospital monitoring for the first 10 days. Such an approach should still be used very cautiously and only when treatment alternative is unavailable, after a careful assessment of the risk and benefit of the treatment, and after being well discussed with the patient (and parent if a child) and informed consent obtained.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

We declare that all research was performed in adherence to ethical standards.

Statement of Informed Consent

Parents signed a consent form and were explained in detail about the procedures and risks before starting the tolerance induction protocol.

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