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Letter to the Editor

Successful rapid intravenous desensitization to rifampicin in a patient with tuberculosis

Federico Spataro[1 #], Roberto Ria[2 #], Mattia Cristallo[3], Lucia Indrio[3], Vanessa Desantis[1], Angelo Vacca[2], Antonio G Solimando[2], Attilio Di Girolamo[3]

[1] Department of Precision and Regenerative Medicine and Ionian Area — DiMePRe-J, Section of Pharmacology, School of Medicine, University of Bari Aldo Moro, 70124 Bari, Italy
[2] Department of Precision and Regenerative Medicine and Ionian Area — DiMePRe-J, Guido Baccelli Unit of Internal Medicine, School of Medicine, University of Bari Aldo Moro, 70124 Bari, Italy
[3] Department of Precision and Regenerative Medicine and Ionian Area — DiMePRe-J, Post Graduate School in Allergology and Internal Medicine, Guido Baccelli Unit of Internal Medicine, School of Medicine, University of Bari Aldo Moro, 70124 Bari, Italy

# Authors contributed equally to this work.

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Dear Editor,

Pulmonary tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health burden due to its high incidence, transmissibility, and risk of severe complications if inadequately treated [1]. Effective therapy relies on multidrug regimens to ensure bactericidal activity, prevent resistance, and reduce relapse. Rifampicin is a key first-line agent for its potent bactericidal effect and ability to sterilize persistent bacilli, playing a decisive role in treatment success [2]. However, hypersensitivity reactions (HR) to rifampicin, though uncommon, represent a significant clinical challenge [3]. These range from mild cutaneous eruptions to severe immediate reactions such as urticaria, angioedema, or anaphylaxis, often necessitating drug discontinuation and compromising therapy, as alternatives may be less effective or more toxic. In such cases, desensitization can be a valuable option. This involves the stepwise administration of increasing drug doses to induce temporary tolerance under close supervision [4]. The mechanism likely reflects transient mast cell and basophil hyporesponsiveness with reduced mediator release [5]. Desensitization has been successfully applied to several drug classes, including antibiotics, antivirals, chemotherapeutics, and recombinant enzymes [6–9].

Herein, we describe the case of a 61-year-old man with rifampicin hypersensitivity who underwent successful rapid desensitization, allowing continuation of essential antitubercular therapy.

The patient's past medical history included thrombotic thrombocytopenic purpura diagnosed in 2020, treated with corticosteroids, plasmapheresis, and caplacizumab, the last dose of which was administered in early 2024. In September 2023, he was diagnosed with pulmonary TB. Standard therapy with rifampicin, isoniazid, pyrazinamide, and ethambutol was initiated; but discontinued after one month due to severe hepatotoxicity with glutamic-pyruvic transaminase (GPT) 280 U/L, glutamic-oxalacetic transaminase (GOT) 250 U/L, and total bilirubin 2.1 mg/dL.

After the hepatic function normalized, antitubercular therapy was reintroduced in November 2023, this time excluding pyrazinamide. Despite initial clinical improvement, the patient developed a generalized maculopapular rash and renewed hepatotoxicity after one month, prompting another suspension of treatment. Though his condition appeared to stabilize, the patient declined further therapy. However, in December 2024, radiologic imaging revealed new pulmonary infiltrates. A bronchoalveolar lavage performed in January 2025 confirmed TB reactivation.

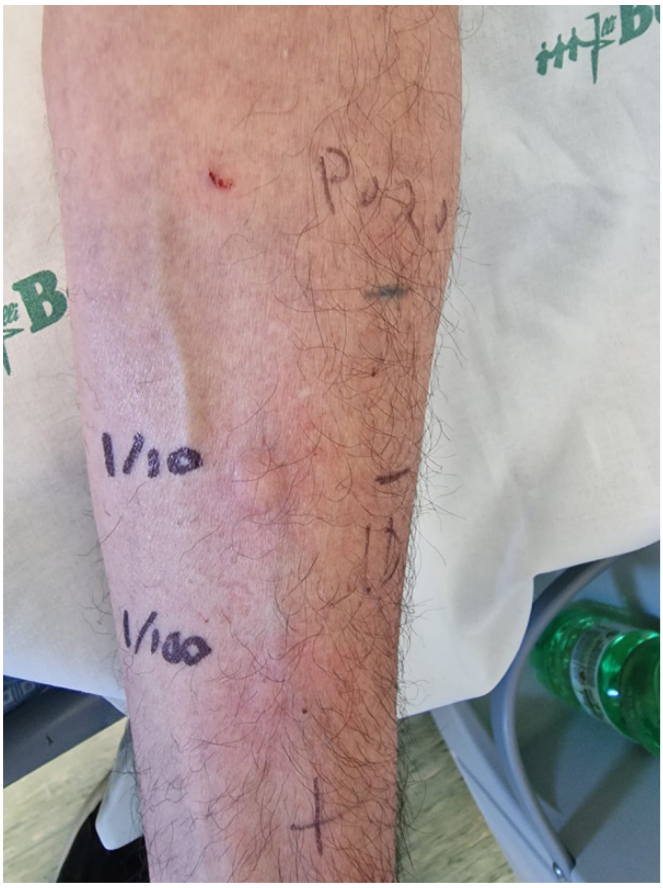
The patient was re-hospitalized on 18 February 2025, with the aim of restarting specific therapy, including intravenous rifampicin and intravenous isoniazid. On 19 February, during the first infusion of rifampicin, he developed an immediate HR characterized by urticaria and intense pruritus. The drug was immediately discontinued, and the reaction was managed successfully with methylprednisolone 40 mg and chlorphenamine 10 mg intravenously. Given the

timing and nature of the symptoms, the reaction was consistent with an immediate HR according to Gell and Coombs classification [10]. Therapy was once again interrupted. It should be noted that the patient experienced two distinct HRs to rifampicin: a generalized maculopapular rash after one month of therapy, consistent with a delayed-type (Type IV) reaction; and an immediate urticarial reaction during infusion, consistent with a Type I (IgE-mediated) reaction. The decision to proceed with rapid desensitization was based on the most recent IgE-mediated reaction.

An allergy work-up was promptly initiated in view of the central role of rifampicin in effective TB treatment and the limited therapeutic alternatives. Skin testing was performed following standard procedures to confirm immediate-type hypersensitivity to rifampicin. Skin prick testing on the volar forearm used a rifampicin solution prepared from the powdered formulation, reconstituted in saline to 60 mg/mL, with histamine and saline as positive and negative controls. Reactions were read after 20 minutes, and the test yielded a negative response. Intradermal testing was then carried out with 1:10 (6 mg/mL) and 1:100 (0.6 mg/mL) dilutions, prepared by serial dilution in saline, and 0.02 mL of each injected intradermally. Both dilutions yielded positive responses (average wheal diameters 5 mm and 10 mm), confirming an immediate IgE-mediated hypersensitivity to rifampicin (Figure 1).

The desensitization protocol followed a 12-step, 3-bag intravenous infusion schedule aiming for a target dose of 600 mg rifampicin. Three dilutions were prepared by serial dilution in saline: the 1:1 solution consisted of 600 mg of rifampicin in 500 mL saline (1.2 mg/mL); the 1:10 solution was obtained by diluting 10 mL of the 1:1 solution in 90 mL saline (0.12 mg/mL); and the 1:100 solution by diluting 10 mL of the 1:10 solution in 90 mL saline (0.012 mg/mL). The protocol commenced with the most diluted solution (1:100) and advanced through increasing concentrations and infusion rates. This 3-bag, 12-step protocol was selected in line with standardized desensitization schemes established for other drugs, ensuring a gradual and safe dose escalation. The use of three successive dilutions allowed us to start from a very low

Figure 1. Skin tests results with rifampicin.



Intradermal tests with rifampicin at 1:100 (0.6 mg/mL) and 1:10 (6 mg/mL) dilutions showed immediate positive reactions, with wheal diameters of 5 mm and 10 mm, respectively. Negative skin prick test with undiluted rifampicin.

Table 1. Intravenous desensitization schedule for rifampicin (target dose = 600 mg).

Step	Solution	Infusion rate (mL/h)	Duration (min)	Dose delivered (mg)
1	1/100	4	15	0.012
2	1/100	10	15	0.03
3	1/100	20	15	0.06
4	1/100	40	15	0.12
5	1/10	10	15	0.3
6	1/10	20	15	0.6
7	1/10	40	15	1.2
8	1/10	80	15	2.4
9	1/1	20	15	6.0
10	1/1	40	15	12.0
11	1/1	80	15	24.0
12	1/1	150	182	546.0
Total			347	592.7

Rifampicin 60 mg/mL. 1 vial = 10 mL. Solution 1/1: 1.2 mg/mL (600 mg rifampicin in 490 mL of saline). Solution 1/10: 0.12 mg/mL (prepared by diluting 10 mL of solution 1:1 in 90 mL of saline). Solution 1/100: 0.012 mg/mL (prepared by diluting 10 mL of solution 1:10 in 90 mL of saline).

concentration and progressively increase both concentration and infusion rate until the full therapeutic dose was reached. Premedication with chlorphenamine 10 mg and methylprednisolone 20 mg, intravenously, was administered 30 minutes prior to the procedure (Table 1).

The patient tolerated the entire desensitization protocol without any adverse events and the liver function remained stable with normal values of GPT, GOT, and bilirubin. Rifampicin was then immediately transitioned to oral administration and continued daily without recurrence of HR. Liver function remained stable, and clinical and radiological improvement was observed in the following weeks.

Although rare, immediate HRs to rifampicin can pose a substantial challenge. This case demonstrated classic features of an IgE-mediated response, confirmed by positive intradermal testing and the clinical characteristics of the reaction. Rifampicin is a cornerstone of TB therapy, yet hypersensitivity reactions can pose a significant clinical challenge, potentially compromising treatment efficacy. Management of these reactions requires a targeted approach, and drug desensitization represents a well-established strategy to allow continued therapy in patients with immediate-type reactions.

To date, literature reports on rifampicin desensitization are limited and have almost exclusively described oral desensitization protocols [11]. In a recent large case series, Koycu Buhari *et al.* reported successful oral desensitizations in patients with immediate-type HRs to first-line anti-TB drugs, including rifampicin, achieving a high rate of tolerance through structured readministration protocols [12]. These protocols, while effective, generally require longer treatment times, stepwise oral dose escalation, and are therefore less applicable in acute or hospital settings where rapid reinstatement of therapy is required.

Moreover, a previous attempt at intravenous desensitization by Dutau *et al.* was ultimately unsuccessful, as tolerance was not maintained after subsequent oral rifampicin administration, resulting in relapse of hypersensitivity symptoms including cutaneous eruption [13]. In contrast to that report, this case highlights a successful outcome following intravenous desensitization, with immediate and sustained oral rechallenge. In the case described by Dutau *et al.*, tolerance was initially achieved through intravenous desensitization, but hypersensitivity recurred soon after reintroduction of oral rifampicin, presenting with urticaria, hepatitis, and proteinuria. The authors suggested that the delayed onset and systemic involvement indicated a non-IgE-mediated mechanism, which may explain the failure of desensitization. Moreover, details of their protocol were not provided, limiting direct comparison. In contrast, our patient developed a classic immediate urticarial reaction during infusion, supported by positive intradermal tests, consistent with IgE-mediated hypersensitivity. Although rare, patients may exhibit more than one type of hypersensitivity to the same drug. In our case, the most recent reaction was an immediate IgE-mediated event, justifying rapid desensitization. The sustained success of our approach likely reflects the structured 12-step, 3-bag protocol, corticosteroid and antihistamine premedication, immediate transition to oral rifampicin, and the absence of systemic organ involvement or allergic comorbidities. These factors may explain the long-lasting tolerance achieved compared with the unsuccessful outcome reported by Dutau *et al*. This result supports the hypothesis of a true IgE-mediated mechanism in our patient, responsive to desensitization, and demonstrates the feasibility of transitioning directly to oral therapy post-procedure in selected patients.

The immunologic basis of rapid desensitization remains only partially understood. The most accepted hypothesis is that incremental exposure to sub-therapeutic doses of the allergen leads to temporary mast cell and basophil hyporesponsiveness, possibly by altering intracellular signaling or receptor sensitivity [5]. While these mechanisms are intriguing, they remain speculative in the context of our case, as no immunologic monitoring was performed. Nonetheless, the sustained tolerance observed after both intravenous and oral rifampicin administration suggests that a true IgE-mediated response was successfully attenuated by desensitization.

Although rifampicin desensitization is not yet standardized, our protocol aligns with existing models used for other medications such as antibiotics, chemotherapeutic and enzymes agents, typically involving 12 steps over several hours [6–9,14]. The success of this approach in our patient supports its broader application, especially in high-risk patients for whom rifampicin remains indispensable for TB treatment.

This report is based on a single patient, which inherently limits the generalizability of our findings and precludes firm conclusions regarding the broader applicability of the desensitization protocol. No drug-specific in vitro tests, such as basophil activation assays or specific IgE for rifampicin, were performed; while

these could provide additional mechanistic insight, they are not standardized or widely validated for rifampicin, and their absence limits immunologic confirmation beyond skin testing. Although the patient tolerated both intravenous desensitization and subsequent oral therapy without recurrence of hypersensitivity, the long-term safety and durability of tolerance remain uncertain.

In conclusion, this case illustrates the effectiveness and safety of rapid intravenous desensitization to rifampicin in a patient with confirmed immediate hypersensitivity. The successful switch to oral rifampicin without adverse reactions further supports the robustness of the desensitization process. By critically comparing our case to existing literature, it appears that protocol structure, premedication, timing, and patient characteristics—together with the underlying IgE-mediated mechanism—may all have contributed to the positive outcome.

Given the vital role of rifampicin in TB management, this approach may offer a practical and life-saving alternative to drug discontinuation. Further research is warranted to define standardized protocols and to better elucidate the immunological mechanisms underlying desensitization.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

FS and ADG, conceived the desensitization approach; MC and LI, carried out the clinical work; FS and ADG, wrote the first manuscript draft; VD, AV, AGS, and RR, critically reviewed and edited the manuscript, and secured financial support. All authors have read and approved the manuscript.

Corresponding author

Mattia Cristallo, MD.
Department of Precision and Regenerative Medicine and Ionian Area - DiMePRe-J, Post Graduate School in Allergology and Internal Medicine, Guido Baccelli Unit of Internal Medicine, School of Medicine, University of Bari Aldo Moro, 70124 Bari, Italy.
Tel: +39 0805592701
Email: cristallomattia@gmail.com

Conflict of interest

No conflict of interest is declared.

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