

# Can a Drug-Induced Pulmonary Hypersensitivity Reaction Be Dose-Dependent?

## A Case with Mesalamine

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### Abstract

Mesalamine-induced pulmonary adverse drug reactions (ADRs) in the course of therapy for inflammatory bowel diseases are rare events, having been reported in only 21 cases. This response, resembling hypersensitivity pneumonitis, is considered to be immunologically mediated and thus dose-independent. We report the case of a 70-year-old woman with ulcerative colitis (UC) who developed biopsy-proven interstitial pulmonary disease (lymphocytic alveolitis and mild interstitial pulmonary fibrosis) three months after starting mesalamine therapy.

The usual treatment in cases of ADR is cessation of the drug and initiation of corticosteroids. In this case, we continued the mesalamine therapy but halved the dose, and did not add corticosteroids. This approach led to a remission of the pulmonary manifestations without a resurgence of UC symptoms.

Based on a review of the literature and our own observation, we challenge the concept that mesalamine-induced pulmonary injury is always due to a hypersensitivity reaction. The evidence suggests that in some cases pulmonary ADR is dose-related; in such instances the most accepted therapy is not necessarily the most appropriate one.

**Key Words:** Mesalamine, ulcerative colitis, adverse drug reaction, pulmonary manifestations, hypersensitivity reaction.

### Introduction

SULFASALAZINE and 5-aminosalicylic acid (5-ASA or mesalamine) releasing preparations are commonly used to treat mild or moderately active ulcerative colitis (UC) and Crohn's disease (CD), and to maintain remission (1). However, up to 30% of patients taking 4 g/d of sulfasalazine develop adverse drug reactions (ADRs) (1). These reactions can be categorized as either plasma-concentration-dependent (i.e., they respond to a reduction of the dose), or plasma-concentration-independent (i.e., they do not so respond) (2). Symptoms of dose-dependent reaction include headaches, nausea and fatigue, whereas dose-independent reactions include rashes, hepatitis, nephritis and pneumonitis. The latter reactions are thought to be the manifestations of an allergy (or a hypersensitivity). The terms "drug hypersensitivity" and "drug allergy" are often used to describe the reactions mediated by the immune system (3).

In contrast, mesalamine, which lacks the sulfapyridine moiety considered responsible for most sulfasalazine ADRs, when taken up to 4.8 g/d, appears to induce no more dose-related reactions than does a placebo in a controlled study. Although such reports are infrequent, mesalamine is known to induce hypersensitivity reactions such as nephritis, pancreatitis and pneumonitis (1, 2). In the presence of a hypersensitivity reaction, it is recommended, by many, that the drug be discontinued and corticosteroids be administered (4, 5).

We present our experience with a patient with UC, who, during treatment with oral mesalamine, developed interstitial lung disease (ILD), weakly positive antinuclear antibodies (ANA) and a progressive increase in the value of the nonpancreatic fraction of amylasemia. Once the signs of pulmonary injury became manifest we treated the patient, who was by then in remission of the UC, in an unconventional way. We continued the mesalamine but halved the initial dose, from 2.4 g/d to 1.2 g/d, which was still above the minimum (0.8 g/d) effective maintenance dose suggested. (1, 6). We did not administer corticosteroids. Four years after we reduced the maintenance dose, the patient is still in remission, without any sign of ADR.

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We have reviewed the literature to assess whether an alternative exists to the widely accepted concept that mesalamine-induced pulmonary injury is the result of an immunological or idiosyncratic reaction. A survey of 21 cases showed that in two instances a rechallenge or a continuation of mesalamine therapy did not elicit a recurrence of ADRs, and in three other cases maintenance doses of corticosteroids failed to prevent ADRs. In addition, in about half of the cases, no treatment with corticosteroids showed comparable outcomes to cases in which corticosteroids were administered. Based on these findings, we propose that in some cases the ADRs might not be immunologically mediated, and a rethinking of the therapeutic approach in these special cases might be in order.

### Case Report

A 70-year-old white woman, with a 10-cigarettes-per-day smoking habit, was admitted to the hospital with the following complaints: fever (38°C), abdominal pain and one week of diarrhea containing mucus and blood. She had no pulmonary complaints. Ten years earlier she had been diagnosed with autoimmune hypothyroidism, for which she was receiving therapy with L-thyroxine.

Results of some laboratory tests were as follows: erythrocyte sedimentation rate, 83 mm/hr; C-reactive protein, 9.23 mg/dL; and 2 globulin fraction, 15.2%. ANA and autoantibodies anti-DNA were negative. The chest radiograph was normal (Fig. A).

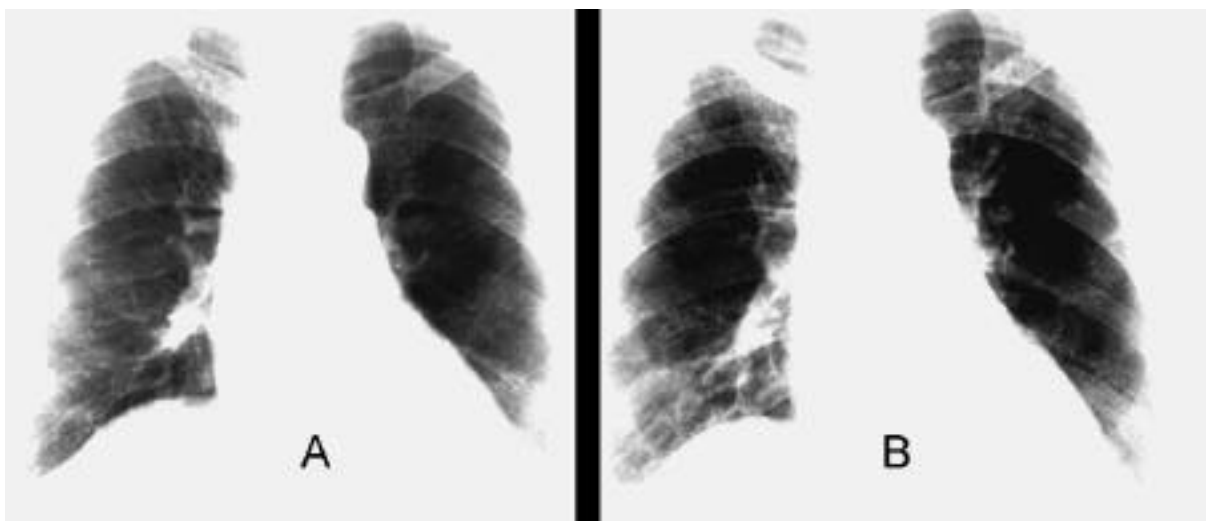
Colonoscopy revealed hyperemic mucosa with pseudopolyps and deep ulcerations extending to all colonic segments; multiple biopsies were consistent with UC (diffuse inflammatory infiltrates, crypt abscesses).

Therapy with prednisone (75 mg/d for 10 days and then gradually tapering off), coated mesalamine (Asacol®) at oral dosage of 2.4 g/d, and ranitidine 300 mg/d was instituted. The therapy resulted in a rapid resolution of symptoms. A colonoscopy performed 2 months later revealed no ulcerations. At this point the corticosteroids were discontinued, while the 5-ASA was maintained at the same dosage.

Three months after beginning the therapy, the patient started complaining of a dry cough and dyspnea on effort. There was no evidence of cardiac disease. Chest x-ray revealed diffuse accentuation of the pulmonary reticulum (Fig. B), and high-resolution computerized tomography (CT) evidenced small, diffuse opacities.

Laboratory results showed pH,  $P_{aO_2}$ ,  $P_{aCO_2}$ ,  $S_{aO_2}$  (oxygen-saturation) and  $HCO_3$  values in arterial blood of 7.46, 49 mm Hg, 39 mm Hg, 86%, and 28 mmol/L respectively. Also noted was the appearance of antinuclear antibodies (ANA) with homogeneous pattern (titre 1:40) and anti-DNA (titre 1:20). Other auto-antibodies, including the antineutrophil cytoplasmic antibodies (ANCA), were absent.

Pulmonary function tests showed a restrictive pattern. Bronchoscopy was negative and examination of the transbronchial lung biopsy showed a thickened interstitium (reticular fibers). The bronchoalveolar lavage (BAL)



**Fig. A.** Normal chest x-ray at the time of admission. **B.** Chest x-ray after 3 months of mesalamine therapy revealed accentuation of pulmonary reticulum. The patient complained of cough and dyspnea.

showed a count of 60% lymphocytes and 40% monocytes. The markers for CD19 and CD3 were 0.35 and 80% respectively, and the CD4/CD8 ratio was 0.39. Mycetes, mycobacteria, or other microorganisms were not found on the lung biopsy sections and on the BAL. There was no eosinophilia. A diagnosis of interstitial pneumonitis (lymphocytic alveolitis) and mild pulmonary fibrosis, consistent with drug-induced lung disease, was made. At this time, colonoscopy did not reveal any acute inflammation and only a few small pseudopolyps.

A decision was made to reduce the daily dose of 5-ASA to 1.2 g. Corticosteroids were not reinstated. Rapid improvement of the respiratory symptoms followed without any recurrence of IBD symptoms.

Two months later, now 5 months after admission, the results of arterial blood gas determinations were within normal limits; the spirometric test was clearly improved; and a repeat chest x-ray showed a reduction of the reticular pattern. Antinuclear and anti-DNA antibody titres were absent.

Five months after the reduction of 5-ASA, now 8 months after the original admission, repeat chest radiographs, CT, bronchoscopy, arterial blood gas studies and pulmonary-function tests all showed normal results. Auto-antibodies were all negative, except for the antithyroid antibodies. BAL contained lymphocytes 30%, monocytes 70%, CD19 1.1%, CD3 69%, and a CD4/CD8 ratio of 1.05.

At the last follow-up, 4 years after the diagnosis of UC, during which time the patient was maintained on the mesalamine therapy, neither UC nor pulmonary manifestations had recurred. Of note, from the beginning of mesalamine therapy, the value of the serum amylase rose gradually to about 400 IU/L (normal values 0–220 IU/L) at 15 months, and fluctuated between 300 and 400 IU/L thereafter. The pancreatic fraction and the serum lipase remained within normal limits. At no time was there clinical or echographic evidence of pancreatitis or alterations of the salivary glands. The ANA titre at this last follow-up was reported to be positive (1:320). The other auto-antibodies, except for the antithyroid antibodies, remained negative.

### Discussion

There are three different 5-ASA delivery systems. Our patient received the eudragit-coated preparation (Asacol<sup>®</sup>); with this prepara-

tion, the active drug is released in the gut by pH. A second preparation is one in which the active drug, encapsulated within ethyl cellulose-coated beads (Pentasa<sup>®</sup>), is released by agitation. The third form, olsalazine (Dipentum<sup>®</sup>), provides 2 molecules of 5-ASA when its diazo bond is broken by the action of colonic bacteria. We cannot exclude the possibility that the coating of the mesalamine preparation taken by our patient may have played a role in her reaction, since there are no data with respect to this matter.

A survey of the literature revealed 21 cases of 5-ASA-associated lung injury (4, 7–22). Also some inflammatory bowel disease (IBD) extraintestinal manifestations are lung-related (interstitial fibrosis, diffuse obstructive disease, bronchiectasis), and it is sometimes difficult to distinguish between disease-related and drug-induced causes (4). The diagnoses of drug-induced lung injury were based on various factors: the appearance of pulmonary symptoms during mesalamine therapy, the absence of any sign of recurrence of the IBD, the absence of concomitant medications, the striking clinical improvement upon removal of the drug, and for some, a history of sulfasalazine hypersensitivity. An additional factor, as in our case, is the lack of signs of recurrence of the pulmonary ADRs upon reduction of the daily dose of mesalamine. We excluded all case reports in which the pulmonary manifestations occurring during mesalamine therapy were interpreted by the author(s) to be disease-related, as well as those with pleurisy or pericarditis without concomitant involvement of the pulmonary parenchyma.

The 22 cases (including our personal observation) are summarized in the Table. There are 7 males and 15 females, with a mean age at the time of pulmonary manifestations of  $46.1 \pm 17.8$  years, a range of 15–72 years, and a preponderance of cases with ulcerative colitis (19/22). The interval between initiation of mesalamine treatment and onset of pulmonary symptoms varies from 2 days to 8 years. Two patients who manifested pulmonary toxicity within several days of treatment had a history of hypersensitivity to sulfasalazine (cases #1 and 2). The most frequent BAL features observed were an increased percentage of either lymphocytes or macrophages, and sometimes of eosinophils, and an inversion of the CD4+/CD8+ ratio (4 out of 7 patients).

Lung biopsies were performed in 13 patients; for 12 cases the histologic findings were consistent with the diagnosis of interstitial lung

**TABLE**  
*Published Cases of Mesalamine-Induced Pulmonary Reaction.*

Case # and Reference	Type of IBD	Age †	5-ASA: Daily dose/ Duration	Prior SAZ therapy/ Toxicity	EOS/ <i>in vitro</i> pertinent tests	BAL: differen./ CD4:CD8 ratio	Lung biopsy/ Findings	5-ASA stopped or n.c.	Steroids given	Lung Recovery
#1 le Gros et al. <sup>7</sup> 1991	UC	54/F	0.75 g/5 days	Yes/ Skin rash	No/ BD+	63% M 23% Ly/ 0.95	No	Yes	No	F
#2 Welte et al. <sup>8</sup> 1991	UC	67/M	1 g/10 days	Yes/ ILD	?/No	No‡	No‡	Yes	Yes	P
#3,4,5 Hesselmann et al. <sup>9</sup> 1991	UC	53/M	?/ ?	?/ ?	Yes/LS+	?	Yes/ILD	Yes	Yes	F <sup>x</sup>
	UC	42/F	?/ >9 months	Yes/ ?	No/LS+	?	Yes/ILD	Yes	Yes	F
	UC	37/F	?/ >15 months	Yes/No	No	Ly/ Inv	No	Yes	Yes	F
#6 Reinoso et al. <sup>10</sup> 1992	UC	64/F	3.6 g/ 37 months then 3.2 g/ 7 months	Yes/ Skin rash	?/No	?	No	Yes	No	P
#7 Lagler et al. <sup>11</sup> 1992	UC	66/M	3 g/ 3 1/2 months	No	No	67% Ly, 30% M/ ?	Yes/ILD	Yes		F
#8,9,10 Camus et al. <sup>4</sup> 1993	UC, Camus #7	20/M	?/ ?	?/ ?	?/No	64% Ly/ 6.0	Yes/ILD	No	No	F
	UC, Camus #22	27/F	?/ ?	?/ ?	?/No	?	Yes/ILD	Yes		F
	UC, Camus #30	24/F	?/ ?	?/ ?	?/No	?	Yes/ILD	Yes	Yes	F
#11 Honeybourne <sup>12</sup> 1994	UC	30/F	1.6 g/7 months	Yes/ Arthralgia	Yes/No	No	Yes/ILD	Yes	No	F
#12 Declerck et al. <sup>13</sup> 1994	UC	45/F	3 g/ 3 months	No	No	46% M, 39% Ly 12% E/ ?	No	Yes	No	F
#13 Muzzi et al. <sup>14</sup> 1995	Crohn	60/F	1.6–2.4 g/ ~ 8 years	Yes/ No	No	55% Ly, 40% M/ 1.74	No	Yes/ 3 weeks only*	No	F
#14 Bitton et al. <sup>15</sup> 1996	UC	32/F months	4 g/9	Yes/ Skin rash	Yes/No	M/ ?	Yes/ILD	Yes	Yes	F
#15 Sviri et al. <sup>16</sup> 1997	Crohn	49/M	1.5–3 g/ 3 1/2 months	No	No	60% Ly, 10% E/ ?	Yes/ILD	Yes/ 3 months**		F
#16 Lazaro et al. <sup>17</sup> 1997	UC	60/M	?/1 month	No	Yes/No	80% M, 10% E/ ?	Yes/ILD	Yes	No	F
#17 Pascual-Lledó et al. <sup>18</sup> — 1997	Crohn	64/F	3 g/2 months	No	No	Ly, E/ Inv	Yes/ negative	Yes	n.c.	F

Case # and Reference	Type of IBD	Age †	5-ASA: Daily dose/Duration	Prior SAZ therapy/Toxicity	EOS/ <i>in vitro</i> pertinent tests	BAL: differen./CD4:CD8 ratio	Lung biopsy/Findings	5-ASA stopped or n.c.	Steroids given	Lung Recovery
#18 Sesin et al. <sup>19</sup> 1998	UC	72/F	1.6–2.4 g/ 3 months	No	No	No	No	Yes	No	F
#19 Tanigawa et al. <sup>20</sup> 1999	UC	35/F	1.5 g/ 40 days	No	Yes/LS+	49% Ly, 43% M, 7.5% E/ 2.09	Yes/ILD	Yes	No	F
#20 Guslandi <sup>21</sup> 1999	UC	29/F	3 g/2 days	No	No	No	No	Yes/ 3weeks ****	Yes	F†
#21 Facchini et al. <sup>22</sup> 1999	UC	15/M	2.8 g/ 4 months	No	No	No	No	Yes	No	F
#22 Personal Observation	UC	70/F	2.4 g/ 3 months	No	No	60% Ly, 40% M/ 0.39	Yes/ILD	No***	No	F

BAL= bronchoalveolar lavage; BD = basophil degranulation test; E = eosinophils; EOS = peripheral eosinophilia; F = full; ILD = interstitial lung disease; Inv = inversion of CD4+/CD8+ ratio; LS = lymphocyte stimulation test; Ly = lymphocytes; M = macrophages/monocytes; P= partial; SAZ = sulfasalazine; ? = data absent/information missing; = increased; n.c. = no change-continued same dosage.

† Age at time of pulmonary symptoms.

‡ But peripheral eosinophilia, lymphocytic and eosinophilic alveolitis on BAL, and ILD on lung biopsy were reported during sulfasalazine therapy, which was discontinued 7 m earlier.

\* After apparent recovery, patient had incidental finding of lung cancer.

\* After a 3-week interruption, 5-ASA was resumed at the same dose, eliciting no adverse reactions.

\*\* After a 3-month interruption, while receiving steroids, 5-ASA (4 g/day) was resumed, eliciting, 48 hrs later, pulmonary symptoms.

\*\*\* But halved the dose of 5-ASA.

\*\*\*\* After a 3-week interruption, 5-ASA was resumed (0.5 g/day for 5 days and 1g/day for 2 days), eliciting pulmonary symptoms.

† The patient had only pulmonary symptoms but no radiological alterations.

disease. Only normal tissue was seen in the remaining patient. The preponderance of ILD contrasts with the variety of pulmonary complications secondary to IBD; these include, in addition, tracheal obstruction, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, chronic bronchiolitis, diffuse lung disease, and necrotic parenchymal nodules (4).

The prognosis in cases of mesalamine-induced pulmonary ADR is good; in contrast to cases of sulfasalazine-induced lung injuries, no deaths have been reported.

As can be seen from the Table, once pulmonary manifestations were suspected to be mesalamine-induced, a majority of the authors opted to withdraw the drug, and half instituted or continued to use corticosteroids at higher doses, probably assuming that toxicity was due to an allergic reaction and was not dose-depen-

dent. Yet, how strong is the basis for assuming that mesalamine-induced pulmonary injury is due to a hypersensitivity reaction? Two findings from the data support the view that, in some cases, the ADRs are not immunologically mediated.

First, in one patient a rechallenge clearly did not elicit a recurrence of ADRs. In two other patients, a continuation of the mesalamine therapy (at the same or lower dose) did not elicit a recurrence of the ADR. A rechallenge with mesalamine was tried in three other patients. In one of these (#15), after a 3-month interruption while receiving steroids, 5-ASA at higher doses (4 g/d) was resumed, eliciting a recurrence of the pulmonary symptoms 48 hrs later. In another patient (#20), after a 3-week interval, mesalamine was restarted at 500 mg daily for 5 days, without a reaction. Two days

after the dosage was increased (1000 mg/day), the patient exhibited respiratory distress. In contrast, the third patient (#13), after a 3-week interval, resumed 5-ASA at the same dose (1.6 g/d), without corticosteroids. No adverse reactions were experienced. Laboratory test values remained in the normal range. While technically not subject to rechallenge, our patient and one of the patients of Camus et al. (#8) reacted similarly to patient #13. Camus' patient was diagnosed as having an ILD while receiving mesalamine. Because he was complaining of only mild pulmonary symptoms, it was decided to continue the 5-ASA treatment at the same dose, and although steroids were not added, he recovered completely over the following two months.

Second, maintenance doses of corticosteroids did not prevent drug-induced pneumonitis in four patients (cases #7, 9, 17 and 21). In addition, the patient reported by Svirj et al. (#15), failed to improve after high doses of hydrocortisone were administered intravenously (300 mg/d for 3 days), and mesalamine therapy was discontinued. The outcome in about 50% of the patients who were not treated with corticosteroids once the ADRs became evident was identical to that of those who were treated with corticosteroids.

Any conclusion on pulmonary ADR is subject to the limitation that the data are obtained solely from case reports. It is evident from the above observations that several case reports do not fit into the basic immunologic parameters and that, for some, mesalamine-induced toxicity appears to be dose-dependent. Although the essential elements of pathogenesis are unknown (23), we advance the hypothesis that there exist two mechanisms, probably interdependent, for the pulmonary ADR: one is a direct, dose-dependent toxicity mechanism, the other is immunologically mediated. Martin (24) has suggested the same for amiodarone-induced pulmonary injury. Whether such a dual mechanism can be extended to other ADRs is an interesting question that needs to be researched.

If our conclusions are correct, then a rethinking of ADR classifications might be in order. Patterson et al. (25) — as modified by DeSwarte (26) and Blass and deShazo (27) — have devised a classification which groups ADRs into two major categories: predictable and unpredictable reactions. The predictable ADRs include toxicity from overdose and side effects and are dose- or concentration-depen-

dent. The unpredictable ADRs include reactions with a known or presumed immunological basis and are typically dose-independent. These reactions, although unpredictable, result in predictable patterns of organ-specific (skin, lung, liver, heart, etc.) or systemic hypersensitivity that usually recur on subsequent exposure to the drug (28). The mechanisms whereby such apparent immune activation occurs remain speculative. Once a drug-induced pulmonary injury is labeled as a hypersensitivity reaction it will be classified in the "unpredictable" category (29). For some of the reactions it is possible to demonstrate a dose-dependency, and it might be more correct to classify these among the "predictable" group, despite their rarity.

Moreover, it is interesting to note the positive ANA titre for our patient four years after the beginning of mesalamine therapy. However, whether her ADR was an autoimmune response or drug-induced is unclear, since this patient also was found to have autoimmune hypothyroidism.

### Summary

In the cases reviewed, pulmonary manifestations associated with mesalamine-induced ADRs usually regressed completely following whatever therapeutic choices were instituted. There were no deaths. These results suggest a rethinking of the therapeutic approach for some patients whose pulmonary manifestations improve following a reduction in their dose of mesalamine (e.g., to 0.8–1.2 g/d). If there is no ADR, it may be reasonable to continue the use of mesalamine at this dose. The addition of corticosteroids does not seem to be necessary for these patients.

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