

Management of Allergic Reactions to Oxaliplatin in Colorectal Cancer Patients

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Oxaliplatin (Eloxatin) is a third-generation platinum compound that is widely used to treat colorectal cancer. The drug usually is given in combination with 5-fluorouracil (5-FU) and leucovorin (LV) as one part of the FOLFOX regimens, which have shown efficacy in several large-scale clinical trials.¹⁻⁵ Allergic reactions and hypersensitivity to oxaliplatin are chronic adverse events that usually manifest as type I reactions and that are characterized by cutaneous, respiratory, and digestive symptoms. Such allergic reactions have been reported in 2%–15% of treated patients; in 2%–3% of cases, these reactions are severe to life-threatening.⁶⁻⁹

Allergic reactions to other platinum compounds (eg, cisplatin, carboplatin) have been reported mainly in the gynecology field; the role of type I allergy in such reactions has been suggested. According to the literature, hypersensitivity to cisplatin and carboplatin occurs in 5%–27% of treated patients and increases as more courses are given.¹⁰⁻¹⁹ Reactions occur within several minutes of starting administration. In contrast to prevention of taxane allergy, prophylaxis of hypersensitivity reactions to platinum compounds using steroids and/or antihistamines is not very effective.¹⁰⁻¹⁹

The number of Japanese clinical reports about al-

Abstract Allergic reactions to oxaliplatin (Eloxatin) may be sufficiently severe to prevent patients from continuing treatment. Oxaliplatin is a key drug that improves the survival of colorectal cancer patients; however, a uniform approach to prevent allergic reactions in patients using this drug has not been established. We investigated the safety and efficacy of our own preventive strategy in colorectal cancer patients receiving the 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX4) regimen. Each patient received the primary prevention regimen before oxaliplatin infusion during the first cycle and diphenhydramine after cycle 4. Patients who experienced grade 1 or 2 allergic reactions subsequently received the secondary prevention regimen with a higher dose of dexamethasone and prolonged oxaliplatin infusion to allow continued treatment. Oxaliplatin was discontinued in patients with grade 3 or 4 allergic reactions. Forty-eight patients (17.6%) developed allergic reactions, and 30 patients underwent retreatment with the secondary prevention regimen. Nineteen patients (63.3%) showed no reactions during at least 2 cycles; most could be treated for 4 months longer than could patients who did not respond to secondary prevention. This preventive strategy was both safe and effective, allowing patients to continue treatment without detriment to their quality of life.

lergic reactions to oxaliplatin is not large, because the incidence of such reactions is not high; further, the drug was introduced in Japan only a few years ago. Allergic reactions account for approximately 10% of all adverse events, and just 5% of related grade 3/4 events, reported for this platinum drug. They rarely occur after the first dose of oxaliplatin; generally, they develop after about 6 cycles.^{6,7,20} In the Multi-center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial,^{8,9} allergic reactions occurred in 10.6% of treated patients, although only 2.9% suffered grade 3/4 events.

The pathophysiology of these allergic reactions has not been clarified. However, a role of immunoglobulin E-mediated, type I allergy resulting from sensitization during previous cycles often has been suggested, along with some reports of type II allergy.²¹⁻²³ Oligo- or polyclonal T-cell expansion induced by the platinum salt targets a superan-

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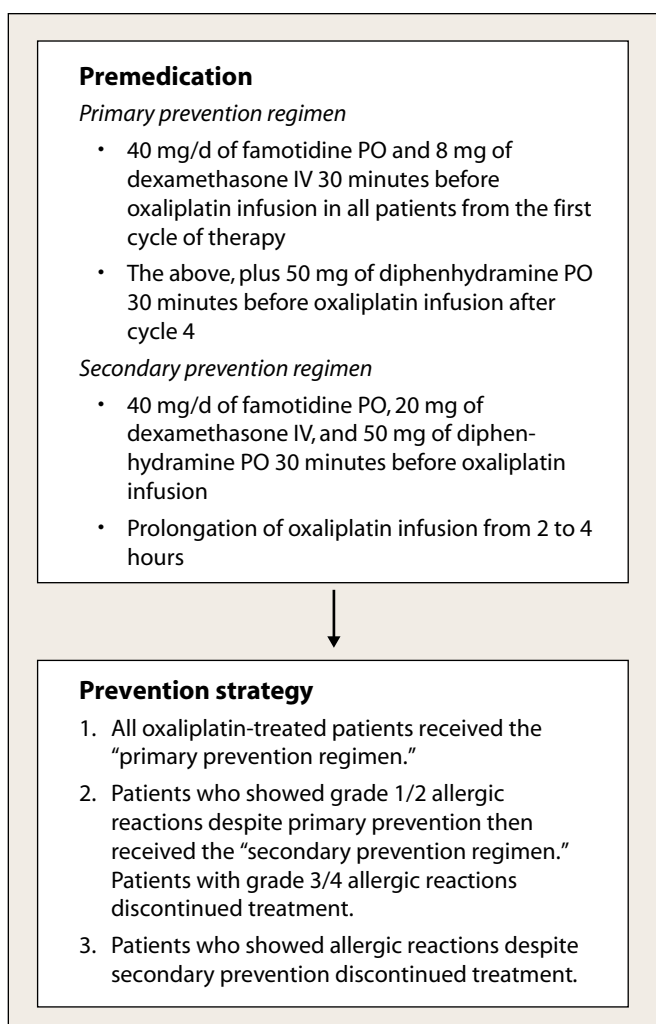


Figure 1 Preventive Strategy Against Allergic Reactions in Patients Receiving 5-Fluorouracil/Leucovorin Plus Oxaliplatin (FOLFOX4) Therapy

Abbreviations: PO = orally; IV = intravenously

tigen on peripheral blood mononuclear cells, leading to the release of pro-inflammatory cytokines. The existence of other unknown binding proteins also has been suggested.^{24,25}

The incidence of neurotoxicity, the dose-limiting toxicity of oxaliplatin, increases in a cycle-dependent manner, and severe symptoms and allergic reactions may necessitate discontinuation of the drug.²⁶ Tumor progression also may be a factor that promotes allergic reactions, since cytokines or binding proteins may be released and may stimulate the immune system.

The onset of most allergic reactions occurs within several minutes after the start of oxaliplatin infusion, and the reaction usually resolves within 2 hours. Cutaneous symptoms are most common, followed by respiratory symptoms, digestive reactions, and generalized reactions. The majority of reactions are grade 1/2, although a few severe reactions (eg, anaphylactic shock) and, rarely, death may occur.

Treatment of allergic reactions usually involves stopping

the oxaliplatin infusion and administering antihistamines and/or steroids. Subsequent management is more controversial. Discontinuation of oxaliplatin therapy may be the appropriate approach, but an alternative is discontinuation of therapy in patients with severe allergic reactions; therapy may be continued if a mild-to-moderate reaction occurs and if the patient is expected to benefit from further treatment.^{6,7,9,11} When treatment is continued, patients receive prophylactic therapy (ie, antihistamines and steroids) and/or a longer duration of oxaliplatin infusion. Desensitization may allow continuation of therapy; however, the large number of patients who receive oxaliplatin makes this strategy impractical.²⁷

After oxaliplatin was approved in Japan in March 2005, we encountered allergic reactions, including some severe cases, in approximately 18% of our patients. The occurrence of severe reactions prompted us to monitor our patients carefully for all allergic reactions, particularly during ambulatory therapy.

This research was designed to evaluate the safety and efficacy of two regimens given to prevent allergic reactions in colorectal cancer patients receiving oxaliplatin at our hospital. We also investigated possible risk factors for allergic reactions, including advanced neurotoxicity and tumor progression.

Methods

PARTICIPANTS

The enrollment criteria for this study follow: histologically confirmed colorectal cancer, advanced metastatic disease, age up to 75 years, Eastern Cooperative Oncology Group performance status of 0–2, and no prior use of oxaliplatin. The treatment protocol was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

TREATMENT REGIMEN

From April 2005 to August 2006, patients were treated with the oxaliplatin-based 5-FU/LV plus oxaliplatin (FOLFOX4) regimen as first-line or subsequent therapy. The regimen involved biweekly cycles. On day 1, patients received 85 mg/m² of oxaliplatin infused intravenously (IV) over 2 hours in 250 mL of 5% glucose plus a bolus dose of 400 mg/m² of 5-FU IV and 100 mg/m² of l-leucovorin (l-LV) IV over 2 hours, followed by 600-mg/m² of 5-FU via IV infusion for 22 hours. The same 5-FU plus l-LV regimen was used on day 2.

PREVENTIVE STRATEGY

Our preventive strategy is outlined in Figure 1. The primary regimen involved administration of 40 mg/d of the histamine-2-receptor antagonist famotidine orally (PO) and 8 mg of dexamethasone IV 30 minutes before the oxaliplatin infusion began. This regimen was given to all oxaliplatin-treated patients from the first cycle of therapy; 50 mg of the histamine-1-receptor antagonist diphenhydramine was given PO after cycle 4.

Patients having any allergic reactions in spite of receiving primary prevention then received the secondary prevention regimen, which entailed 40 mg/d of famotidine PO plus 20 mg

Table 1**Baseline Patient Characteristics (n = 48)**

CHARACTERISTIC	VALUE
Gender, n	
Male	27
Female	21
Mean age, years	58
Range, years	34–75
Incidence, n (%)	48/272* (17.6)
Prior chemotherapy, n (%)	
Yes	30 (62.5)
5-Fluorouracil	29 (60.4)
Irinotecan	11 (22.9)
No	18 (37.5)
Allergy history, n (%)	
Yes	17 (35.4)
Iodine	4 (8.3)
Ethanol (for disinfection)	2 (4.2)
Asthma	5 (10.4)
Others	9 (18.8)
No	31 (64.6)
Antitumor effect, n (%) [†]	
Partial response	12 (25.0)
Stable disease	31 (64.6)
Progressive disease	4 (8.3)
Not evaluable	1 (2.1)
Partial response plus stable disease	43 (89.6)
Neurotoxicity, n (%) [†]	
Grade 0	1 (2.1)
Grade 1	38 (79.2)
Grade 2	9 (18.8)

*272 patients treated with FOLFOX4 (5-fluorouracil/leucovorin plus oxaliplatin)

[†]Antitumor effect and neurotoxicity were evaluated when allergic reactions occurred.

of dexamethasone IV and 50 mg of diphenhydramine PO 30 minutes before the oxaliplatin infusion began. In addition, the duration of oxaliplatin infusion was increased from 2 hours to 4 hours for patients within mild (grade 1) to moderate (grade 2) allergic reactions. Oxaliplatin was discontinued in patients with severe (grade 3) or potentially life-threatening/disabling (grade 4) allergic reactions.

EVALUATION OF TOXICITY/EFFICACY

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.²⁸ Data on toxicity and tumor responses were obtained from electronic medical records and examination of films for each patient. The safety of premedication also was assessed from electronic medical records, laboratory results, and vital sign data.

Neurotoxicity and tumor progression were re-evaluated at the time of allergic reaction as possible risk factors for such reactions. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors²⁹; this assessment was based mainly upon computed tomography scans obtained every 3 months.

Table 2**Features of Allergic Reactions (n = 48)**

FEATURE	VALUE
Median number of cycles	9
Range	4–16
Median total dose of oxaliplatin (mg/m ²)	680
Range	255–1,275
Time to onset of symptoms, n (%)	
< 30 min	16 (33.3)
> 30 min	32 (66.7)
Symptoms, n (%)	
Cutaneous reaction	
Redness	41 (85.4)
Pruritus	36 (75.0)
Urticaria	19 (39.6)
Respiratory symptoms	
Dyspnea	7 (14.6)
Decreased arterial oxygen saturation	8 (16.7)
Digestive symptoms *	5 (10.4)
Generalized reaction	
Hypotension	7 (14.6)
Sweating	5 (10.4)
Fever	4 (8.3)
Chills	1 (2.1)
Grade, n (%)	
1	34 (70.8)
2	7 (14.6)
3/4	7 (14.6)
Treatment of allergic reactions, n (%)	
Stopped oxaliplatin infusion	43 (89.6)
Steroids [†]	26 (54.2)
Antihistamine [‡]	17 (35.4)
Rapid fluid infusion	7 (14.6)
Duration of allergic reaction, n (%)	
< 120 min	47 (97.9)
120 min to 24 h	1 (2.1)
> 24 h	0

*Vomiting, nausea, abdominal pain

[†]100 mg of hydrocortisone intravenously[‡]Diphenhydramine or chlorpheniramine**STATISTICAL ANALYSIS**

The chi-square test and Fisher's exact probability test were used to compare categorical data. Differences between the mean values of continuous variables were assessed by the Student's *t*-test and confirmed by the Mann-Whitney *U*-test. In all analyses, a *P* value of less than 0.05 indicated statistical significance.

Results

Among the 272 patients (140 men, 132 women) who were treated with oxaliplatin and the primary-prevention regimen, 48 (17.6%) developed allergic reactions. Their gender, age, prior chemotherapy, and history of allergy were not risk factors for such events. Tumor progression and neurotoxicity also were not related to development of allergic reactions (Table 1).

Table 3

Comparison of Grade 3/4 and Grade 1/2 Reactions (n = 48)

CHARACTERISTIC	GRADE 3/4 (n = 7)	GRADE 1/2 (n = 41)	P VALUE
Gender			
Male	7	20	0.013
Female	0	21	
Mean age, years	55	58	0.554
Range, years	40–75	34–75	
Median cycle number	8	9	
Range	5–12	4–16	0.288
Symptoms, n (%)			
Cutaneous	5 (71.4)	39 (95.1)	0.038
Respiratory	4 (57.1)	7 (17.1)	0.021
Digestive	3 (42.9)	2 (4.9)	0.002
Generalized*	7 (100.0)	4 (9.8)	< 0.001
Hypotension	7 (100.0)	0	< 0.001
Sweating	4 (57.1)	1 (2.4)	< 0.001
Fever	1 (14.3)	3 (7.3)	0.479
Chills	0	1 (2.4)	> 0.999

*Generalized reactions included fever, sweating, chills, malaise, and hypotension.

Features of the allergic reactions are summarized in Table 2. Allergic reactions occurred after a median of 9 cycles (range, 4–16 cycles); the median total dose of oxaliplatin was 680 mg/m² (range, 255–1,275 mg/m²). All allergic reactions were detected within 2 hours of infusion; in 33.3% of patients, they were detected in less than 30 minutes. Skin reactions were observed most frequently, followed by respiratory symptoms. In all, 41 reactions (85.4%) were grade 1 or 2 events, whereas the other 7 reactions (14.6%) were severe, including 1 grade 4 event. Infusion of oxaliplatin was discontinued immediately, except when symptoms were detected initially at the end of the scheduled infusion. Administration of antihistamines or a steroid (eg, hydrocortisone) or rapid fluid infusion was given, as appropriate. Most patients recovered completely within 2 hours. Oxaliplatin infusion was resumed on the same day at the previous rate in two patients and at a slower rate in an additional two patients without recurrence.

Comparison of clinical features between patients with severe allergic reactions and those with grade 1/2 reactions showed that severe reactions only occurred in men ($P = 0.013$); no other significant risk factors were apparent. Respiratory and digestive symptoms and more generalized reactions (eg, hypotension, fever) were more common among patients experiencing severe reactions than among those having grade 1/2 reactions (Table 3).

A total of 30 patients underwent retreatment with oxaliplatin using the secondary prevention regimen. We defined success as prevention of allergic reactions during at least 2 cycles and failure as any lesser outcome. The results obtained with secondary prevention are summarized in Table 4. Allergic reactions occurred in 11 patients (36.7%) within 2 cycles; 3 patients (27.3%) were so affected during the second cycle. Prevention

Table 4

Outcome of the Secondary Prevention Regimen (n = 30)

ALLERGIC REACTION	n (%)
Effective*	19 (63.3)
Ineffective	11 (36.7)
Episodes of prevention in ineffective patients [†]	11
1	8 (72.7)
2	3 (27.3)
Episodes of prevention until discontinuation due to re-allergic reaction in effective patients [‡]	6
< 4	3 (15.8)
4 to < 8	3 (15.8)
8 to < 12	0
12 to < 16	0
≥ 16	0 [§]
Episodes of prevention until discontinuation due to disease progression in effective patients	11
< 4	5 (26.3)
4 to < 8	4 (21.1)
8 to < 12	1 (5.3)
12 to < 16	0
≥ 16	1 [§]
Comparison of second allergic reaction with first in effective patients	6
Equivalent	6
Worse	0
Better	0
Comparison of second allergic reaction with first in ineffective patients [¶]	11
Equivalent	9 (81.8)
Worse	2 (18.2)
Better	0

*Successful prevention for at least two courses was defined as effective.

[†]Almost all additional reactions occurred during the first course among ineffective cases.

[‡]In ineffective patients, prevention usually was successful for at least 4 courses (2 months). Two patients have continued treatment for over 16 courses.

[§]Continuing treatment in 2

[¶]Serious reactions occurred in 2 patients, and 1 had a grade-3 reaction.

was successful for at least 2 cycles in the other 19 patients. Eleven patients discontinued FOLFOX4 due to tumor progression, and 6 patients discontinued therapy after experiencing allergic reactions during courses 3–6. The other two patients were successfully treated a total of 16 and 22 times, respectively. In the 11 patients for whom prophylaxis failed, a comparison of the reactions occurring during primary and secondary prophylaxis showed that two patients had worse reactions after secondary prophylaxis, and one had a grade-3 reaction.

The safety of the premedications is summarized in Table 5. Drowsiness due to diphenhydramine was observed in two patients (4.2%), and a mild/moderate increase of blood pressure associated with 8 mg or 20 mg of dexamethasone occurred in three patients (6.3%) and 2 patients (6.7%), respectively. There was no cytopenia nor neurologic or digestive manifestations caused by famotidine in any of the patients. No other severe reactions occurred, and there were no other treatment-related severe adverse events or deaths.

We evaluated the benefit of our secondary prevention

regimen by comparing the 19 effective cases with the 11 ineffective cases, as shown in Figure 2. The median number of cycles until the first allergic reaction was 9 in the group for which prevention was effective and 10 in the other group ($P = 0.349$). The median treatment time was 285 days in the effective group versus 164 days in the ineffective group (95% confidence interval: 76–250; $P = 0.0006$).

Discussion

The safety and efficacy of our preventive approach using two regimens for oxaliplatin allergy were evaluated. Comparing our experience with that of previous reports,^{6–9,20} the median number of cycles during which allergic reactions developed and symptoms reported were similar, but the incidence (17.6%) was higher in our patients than in those of previous studies (2%–15%). The overall incidence of allergic reactions was higher in our study than in the MOSAIC trial⁸ (17.6% vs 10.3%, respectively); the same was true for severe reactions (14.6 vs 2.9%, respectively).

Our analysis failed to reveal any risk factors for allergic reactions (eg, history of allergy, occurrence of tumor progression) among patient characteristics. However, there was a significant difference between genders with respect to the risk of severe allergic reactions; this finding must be investigated further in a larger number of patients. In our series, seven patients experienced severe reactions, and they suffered from more symptoms (except cutaneous reactions) than did patients having grade 1/2 reactions. However, these severe reactions all were managed with immediate treatment, and no secondary complications or deaths occurred. To our knowledge, there has been no previous examination of the incidence of grade 3/4 allergic reactions resulting from continued oxaliplatin exposure in patients receiving a specific preventive regimen after experiencing grade 1/2 reactions. Some clinicians at other institutions use preventive methods that are similar to our schemes, but the safety and efficacy of such methods have not been confirmed. Therefore, none of our grade 1/2 patients was assigned to continue FOLFOX4 therapy without prophylaxis because of the risk of complications.

We chose a preventive strategy that included two regimens to promote continuation of therapy, and 63% of our patients showed some benefit. When secondary prevention was successful, most patients (excluding those with tumor progression) could continue FOLFOX4 for 4 or more cycles without experiencing further allergic reactions; these patients were able to receive an additional 4 months of treatment as compared with patients who did not benefit from the strategy.

The outcome of re-exposure to oxaliplatin after a grade-1/2 reaction with or without premedication has been described by several other authors. Brandi et al⁷ reported that 6 of 17 patients having mild allergic reactions were re-exposed to oxaliplatin after receiving premedication with steroids and antihistamines, and 5 of the 6 developed further reactions. Maindault-Goebel et al⁹ studied 42 patients who had allergic reactions to oxaliplatin, and 8 of 15 patients (53.3%) who

Table 5

Safety of the Premedications

DRUG*	SYMPTOMS	n (%)
Diphenhydramine, 50 mg (n = 48)	Headache	2 (4.2)
	Drowsiness	2 (4.2)
	Fatigue	1 (2.1)
	None	44 (91.7)
Dexamethasone, 8 mg for primary prevention (n = 48)	Facial flushing	4 (8.3)
	Insomnia	4 (8.3)
	Increased blood pressure	3 (6.3)
	Fever	3 (6.3)
	Headache	2 (4.2)
	None	36 (75)
Dexamethasone, 20 mg, for secondary prevention (n = 30)	Facial flushing	1 (3.3)
	Increased blood pressure	2 (6.7)
	Fever	2 (6.7)
	None	23 (76.7)

*No symptoms related to famotidine were observed

underwent retreatment with an increased duration of oxaliplatin infusion could continue therapy. Siu et al³⁰ reported that 14 oxaliplatin-allergic patients were re-exposed to the drug after receiving a steroid and chlorpheniramine as premedication; four patients (28.6%) had further reactions, including two patients (14.3%) who had grade 3/4 reactions. According to these studies, both administration of steroids plus antihistamines and prolongation of oxaliplatin infusion were moderately effective in preventing further reactions. However, previous strategies were not uniform, and the details of each protocol and its outcome were not clarified.

When compared with these other studies, our preventive strategy was similarly effective. The strengths of our study included a uniform premedication strategy and a defined prevention plan, which allowed us to evaluate our strategy easily. These results suggested that our strategy allows continued oxaliplatin treatment—therefore, it should be considered an option for preventing allergic reactions to this drug. However, this study also demonstrated that prolonged oxaliplatin treatment

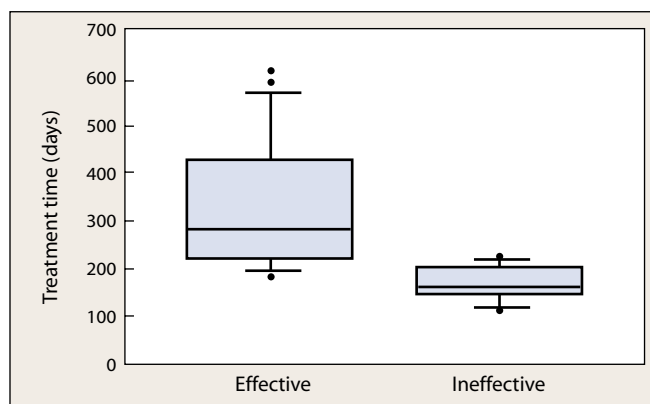


Figure 2 Benefit of the Secondary Prevention Regimen

The median treatment time for the effective and ineffective groups was 285 days and 164 days, respectively (95% confidence interval: 76–250; $P = 0.0006$).

resulted in a continued increase in the risk of allergic reactions. Therefore, to lessen the risk of allergic reactions to oxaliplatin, it seems prudent to limit the treatment period to 4–4.5 months (8 or 9 cycles of FOLFOX4; total dose, 680–765 mg/m²). This recommendation allows patients enough time to achieve the maximum tumor response, as it helps them to avoid severe neurotoxicity²⁶ and diminishes the risk of allergic reactions.

In previous studies, the median time to tumor response was 9 weeks in patients treated with FOLFOX4²; patients receiving oxaliplatin experienced severe neurotoxicity after a cumulative dose of 780–850 mg/m². In our study, nine patients developed

grade 2 neurotoxicity after a median of 4 months (8 cycles of FOLFOX4) and a median total dose of 676 mg/m² (range, 340–1,105 mg/m²) without experiencing any severe allergic reactions. We still are investigating predictors of allergic reactions to oxaliplatin that may enable us to avoid severe reactions.

In conclusion, severe reactions to oxaliplatin generally are manageable if appropriate treatment is provided immediately. Oxaliplatin-based chemotherapy will continue to be first-line treatment for various cancers. Therefore, an appropriate strategy to prevent such allergic adverse reactions should be devised and assessed in a larger trial.

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