ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.5578/aai.10890
Asthma Allergy Immunol 2015;13:130-133

ARAŞTIRMA RESEARCH ARTICLE

Adverse skin reactions caused by L-asparaginase: Allergy or infection?

L-asparajinaz ile gelişen cilt reaksiyonları: Allerji mi, infeksiyon mu?

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ABSTRACT

Objective: L-asparaginase (L-ASP) is one of the indispensible medications used in the treatment of acute lymphoblastic leukemia (ALL); however, the allergic reactions caused by the drug limit its use. 52 patients (37 were low risk, 15 were high risk) who were followed for ALL between January 2010 and July 2014 and who developed local and systemic reactions associated with *Escherichia coli* L-ASP were evaluated.

Results: Of the 52 patients with ALL who underwent therapy according to the St Jude Total XV chemotherapy protocol, three patients developed systemic allergic reaction (anaphylaxis) and eight developed swelling, erythema and increased skin temperatures at the injection site and as well as systemic fever (> 38°C) after *E. coli* L-ASP therapy. All of the patients were treated with pegylated *E. coli* asparaginase, and none reported complaints during the follow-up.

Conclusion: The local reactions in these cases were regarded as allergic due to the recurrence upon challenge and the recovery after different drugs were prescribed; and these reactions occurred particularly in the low-risk group who were receiving the drug every other day in re-induction I.

(Asthma Allergy Immunol 2015;13:130-133)

Key words: Acute lymphoblastic leukemia, Drug allergy, L-asparaginase allergy, drug reactions

Received: 07/10/2015 • **Accepted:** 18/01/2016

ÖZ

Giriş: L-asparajinaz akut lenfoblastik lösemi (ALL) tedavisinde kullanılan vazgeçilemez ilaçlardandır fakat ilaca bağlı allerjik reaksiyonlar bu ilacın kullanılmasını kısıtlamaktadır. Ocak 2010 ile Temmuz 2014 tarihleri arasında ALL sebebiyle takip edilen 52 hasta (37'si düşük risk ALL, 15'i yüksek risk ALL) çalışmaya alındı ve *Escherichia coli* L-ASP'a bağlı gelişen lokal ya da sistemik reaksiyonlar açısından değerlendirildi.

Bulgular: ALL tanısıyla takip edilen ve St. Jude Total XV kemoterapi protokolü alan 52 hastada *E. coli* L-ASP uygulanımı sonrasında üçünde sistemik allerjik reaksiyon (anafilaksi) gelişirken, sekiz hastada enjeksiyon bölgesinde şişlik, kızarıklık, lokal ısı artışı ve sistemik ateş (> 38°C) gözlendi. Hastaların tedavisine pegylated- *E. coli* L-ASP ile devam edildi ve hastaların takibinde ilaca bağlı reaksiyon gözlenmedi.

Sonuç: Hastadaki lokal reaksiyonların ilacın tekrar uygulamaları ile yenilemesi fakat farklı bir ilaca geçildikten sonra gözlenmemesi öncelikle ilaca bağlı allerjik reaksiyonu düşündürdü. Bu reaksiyonlar özellikle düşük risk ALL tanısıyla takip edilen, re-indüksiyon I tedavi protokolünde ilacı gün aşırı alan hastalarda daha sıklıkla görülmektedir.

(Asthma Allergy Immunol 2015;13:130-133)

Anahtar kelimeler: Akut lenfoblastik lösemi, L-asparajinaz allerjisi, kemoterapotik allerjisi

Geliş Tarihi: 07/10/2015 • **Kabul Ediliş Tarihi:** 18/01/2016

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INTRODUCTION

L-asparaginase (L-ASP) is one of the essential medications used in the treatment of acute lymphoblastic leukemia (ALL). The most common side-effects associated with L-ASP include anaphylaxis, hypertriglyceridemia, hyperglycemia, thrombosis, consumption coagulopathy and allergic reactions[1-3].

Asparaginases are prepared from bacteria such as *Escherichia coli* or Erwinia chrysanthemi, and thus humans are able to develop anti-asparaginase antibodies against this foreign material[4]. Antibodies against asparaginase are released from B-lymphocytes upon the stimulation of the immune system by this allergen[5].

The incidence rates reported for *E. coli* asparaginase-associated hypersensitivity reactions range from 0-45 percent[5,6]. Allergic or hypersensitivity reactions often include mild urticaria, fever, localized erythema and pain at the injection site, but may also be more severe, such as systemic anaphylaxis[7].

In this study, the relationship of the reactions (leg pains, soft tissue edema and erythema at the injection site, pain, systemic fever after L-ASP injection) occurring in eight patients who were followed for ALL were evaluated.

MATERIALS and METHODS

This is a prospective study including 52 patients who were followed at pediatric hematology-oncology clinic between January 2010 and July 2014 and diagnosed with acute lymphoblastic leukemia (37 cases with low risk, 15 cases with high risk). All cases underwent therapy according to the St Jude total XV chemotherapy protocol, according to which, the low-risk group received a total of 24 doses, involving six doses of 10.000 U/m^2 every other day in remission-induction therapy, and nine doses of 10.000 U/m^2 every other day during re-induction I and re-induction II. The high-risk group, on the other hand, received a total of 25 IM doses of L-ASP, involving six doses of 10.000 U/m^2 every other day in remission-induction therapy, as well as weekly doses of 20.000 U/m^2 for 19 weeks during maintenance therapy, including re-induction I and II therapies. The cases with systemic allergic reactions including respiratory system involvement were directly changed to an alternative drug. In all cases with local reaction with L-ASP at the injection site, a skin prick test was performed with *E. coli* L-ASP (Leunase© 10000 U /2 mL) at concentrations of 500 U/mL (1/10 concentration) and 5000 U/mL (1/1 concentration) , and histamine 10 mg/mL and serum physiologic were used as positive and negative controls, respectively[8]. A positive skin prick test was considered positive if an induration of 3 mm greater than the negative control at 15 minutes was observed. None of the patients had intradermal testing with L-ASP.

RESULTS

Of the study population, 11 patients had local and/or systemic reactions associated with *E. coli* L-ASP. Among them, three patients developed systemic allergic reactions, manifested in the form of diffuse skin rash and facial swelling, as well as respiratory difficulties, and eight patients developed local reactions including swelling, redness, and increased skin temperature at the injection site with accompanying systemic fever (> 38°C). The patients who developed systemic allergic reactions were followed with a diagnosis of high-risk ALL. The allergic reactions were observed between the 1st and 3rd weeks of the maintenance therapy (total 7-9 doses). Of the eight patients who developed local reactions with accompanying systemic fever, five were males and three were females, aged between 4 and 16 years old. Of them, seven cases had low-risk ALL and one had high-risk ALL. Of the patients with low-risk ALL, six patients developed erythema at the injection site, leg pain and soft tissue edema between the fourth and sixth doses of *E. coli* L-ASP (Leunase, Tokyo, Japan) during re-induction I therapy (total 1-12 doses) and one patient developed similar reactions after the second dose of *E. coli* L-ASP. One patient with high-risk ALL developed erythema, swelling and soft tissue edema at the injection site in the gluteal region after the sixth dose of remission-induction therapy. All cases displayed erythema, which developed 1-2 hours after the IM injection, and leg pain, swelling and difficulty in walking that developed one day after the initial manifestation. An ultrasonography of the edematous area revealed a thickening of the muscles and increased echogenicity associated with inflammation. No abscess, hematoma or fluid build-ups were observed. The patients had fevers above 38°C, and so intravenous antibiotic therapy was administered for 10 days for the treatment of soft tissue infection. All eleven cases with adverse skin reaction with L-asparaginase had skin prick testing with the drug. The two cases with positive skin prick testing were regarded as having developed an IgE-mediated allergic reaction and their therapy was continued with pegylated *E. coli* asparaginase. Although the remaining cases tested negative in the skin prick test, *E. coli* L-ASP therapy was discontinued due to the persistence of similar complaints, despite the pre-treatment with antihistamines one hour prior to the *E. coli* L-ASP administration. In all cases, therapy was continued with pegylated *E. coli* asparaginase (Oncaspar 2500 U/m^2), and none of the patients reported any complaints. The characteristics of the cases are presented in Table 1.

Table 1. General characteristics of the patients with ALL who developed local reactions associated with L-ASP

Case	Age (year)	Gender	Diagnosis	Reaction time (total doses)	IgE (IU/mL)	Skin prick tests
1	6	Boy	low risk ALL	re-induction I, 4-5. doses (10-11doses)	12.46	Positive
2	13	Girl	low risk ALL	re-induction I, 4-5. doses (10-11doses)	10.26	Positive
3	6	Boy	low risk ALL	re-induction I, 4-6. doses (10-12 doses)	10.31	Negative
4	4	Boy	low risk ALL	re-induction I, 2. doses (8 doses)	29.41	Negative
5	4	Girl	low risk ALL	re-induction I, 5-6. doses (11-12 doses)	7.12	Negative
6	15	Girl	low risk ALL	re-induction I, 4-5. doses (10-11 doses)	4.65	Negative
7	10	Boy	low risk ALL	re-induction I, 4. Doses (10 doses)	300.1	Negative
8	16	Boy	high risk ALL	remission-induction, 6. dose	6.8	Negative
9	5	Boy	high risk ALL	maintenance 1. week (7 doses)	-	ND
10	10	Boy	high risk ALL	maintenance 3. Week (9 doses)	-	ND
11	16	Girl	high risk ALL	maintance 3. week (9 doses)	-	ND

ND: Not done.

DISCUSSION

L-ASP is one of the essential drugs in the treatment of ALL. Due to the immunogenic properties of the drug, it can produce allergic reactions in humans, and these reactions can be detrimental to the treatment of the patients. The risk of allergic reaction increases with doses higher than 6000 IU/m^2/day, intravenous administration of the drug and repeated drug doses[9].

According to a report from St Jude Children's Hospital (SJCRH), L-ASP allergies occur in a median at 12^{th} dose (between 3^{rd} and 22^{nd} doses) and mostly during maintenance therapy. In a study by Total 13 Study Group, anti-L-ASP antibodies were found to be elevated after the ninth dose of the induction phase in 54 (35.5%) of 152 patients who had undergone L-ASP therapy. Of the fifty-four children with elevated antibody levels, 30 (55.5%) developed allergic reactions, while only 18 out of 98 children (18.3%) with normal antibody levels developed clinically significant allergies[4].

In the study by Soyer et al., the prevalence of L-ASP allergies during therapy according to the St Jude total XIII protocol was 36.8 percent in the remission-induction phase, 47.9 percent in the maintenance phase and 5.3 percent in the re-induction phase[10]. In the study by Woo et al., the allergic reactions were observed during the maintenance and re-induction phases, and it was suggested that the administration of L-ASP therapy for a period of at least one month increases the risk of allergic reaction[6].

In our study, the complaints of the patients began during the re-induction therapy during which the patients were receiving L-ASP injections every other day. The patients reported problems particularly after the fourth dose of re-induction therapy that was administered every other day (total 10 doses) and the complaints worsened after the ensuing doses. Studies in the literature have reported allergic reactions after the 12^{th} dose of the drug, while in this study, local reactions occurred between the 10^{th} and 12^{th} doses of the drug[4,6].

The reactions reported in the literature in association with L-ASP allergies often include urticaria, angioedema and respiratory symptoms, and these are mostly IgE-mediated type I hypersensitivity reactions [10]. In addition, increases in IgG1, IgG3, IgG4 levels in the peripheral blood have also been reported[11]. In contrast, none of the studies demonstrated a relationship between elevated antibody levels and the allergic reactions associated with L-ASP[11,12].

The cellulitis of the lower leg is a moderately common and unpleasant condition associated with painful erythema and swelling, in some cases high fever, and very rarely shock and cardiovascular collapse[13]. The patients in this study were initially thought to have soft tissue infections and were treated accordingly; however, this local reaction was then found to have been caused by an allergic reaction upon re-challenge with IM L-ASP that caused a further aggravation of the symptoms. Skin prick testing was used to diagnose IgE-mediated type-I hypersensitivity reactions, and all patients underwent a skin prick test with L-ASP, with two patients testing positive, supporting the diagnosis of type-I hypersensitivity reaction. The lack of recurrent reactions during therapy with IM pegylated L-ASP supported the notion that previous reactions were caused by an allergy to L-ASP.

Skin prick tests, which may indicate a type-I hypersensitivity reaction, may show false negative results

in patients presenting with L-ASP allergies[10]. Local allergic reactions are mostly associated with IgG-dependent antibodies, and so it has been suggested that the cases with negative skin prick test results may have developed an IgG-mediated allergic reaction, but it was not possible to demonstrate these antibodies due to technical drawbacks[10].

In conclusion, the local reactions that occurred in patients were considered to be associated with allergies, because the symptoms recur upon re-challenge and recover spontaneously after switching the therapies. Furthermore, allergic reactions mostly occurred between doses 10 and 12, and occurred particularly in the low-risk group during re-induction therapy, involving drug injections every other day. The allergic reactions were considered to be related to IgG and IgE antibodies. It can be suggested that an early evaluation of reactions at the injection site and switching therapies may prevent the development of more serious adverse reactions.

REFERENCES

1. *Cremer P, Lakomek M, Beck W, Prindull G. The effect of L-asparaginase on lipid metabolism during induction chemotherapy of childhood lymphoblastic leukaemia. Eur J Pediatr 1988;147:64-7.*
2. *Weiss RB. Hypersensitivity reactions. Semin Oncol 1992;19:458-77.*
3. *Clavell LA, Gelber RD, Cohen HJ, Hitchcock-Bryan S, Cassady JR, Tarbell NJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med 1986;315:657-63.*
4. *Raetz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010;32:554-63.*
5. *Shinnick SE, Browning ML, Koontz SE. Managing hypersensitivity to asparaginase in pediatrics, adolescents, and young adults. J Pediatr Oncol Nurs 2013;30:63-77.*
6. *Woo MH, Hak LJ, Storm MC, Sandlund JT, Ribeiro RC, Rivera GK, et al. Hypersensitivity or development of antibodies to asparaginase does not impact treatment outcome of childhood acute lymphoblastic leukemia. J Clin Oncol 2000;18:1525-32.*
7. *Liu C, Kawedia JD, Cheng C, Pei D, Fernandez CA, Cai X, et al. Clinical utility and implications of asparaginase antibodies in acute lymphoblastic leukemia. Leukemia 2012;26:2303-9.*
8. *Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.*
9. *Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. Critical reviews in oncology/hematology 2007;61:208-21.*
10. *Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. J Allergy Clin Immunol 2009;123:895-9.*
11. *Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. Critical reviews in oncology/hematology 1998;28:97-113.*
12. *Fabry U, Korholz D, Jurgens H, Gobel U, Wahn V. Anaphylaxis to L-asparaginase during treatment for acute lymphoblastic leukemia in children-evidence of a complement-mediated mechanism. Pediatric Research 1985;19:400-8.*
13. *Hay RJ. Preventing cellulitis: where next? Br J Dermatol 2014;171:1304-6.*