Review

Shilpa Mehta, Vikash Oza, Renee Potashner, Patricia Zamora, Manish Raisingani and Bina Shah*

Allergic and non-allergic skin reactions associated with growth hormone therapy: elucidation of causative agents

https://doi.org/10.1515/jpem-2017-0309
Received August 8, 2017; accepted October 30, 2017; previously published online December 2, 2017

Abstract

Background: Allergic and non-allergic skin reactions to recombinant human growth hormone (rhGH) are uncommon and infrequently reported. However, physicians should be aware of these potential side effects to determine whether the reactions constitute true allergies and how to proceed with growth hormone therapy. To review allergic and non-allergic skin reactions caused by rhGH and subsequent diagnostic workup and management options.
Case presentation: We report the case of a 12-year-old healthy male presenting with idiopathic short stature. He developed an itchy skin rash over the chest and abdomen, 15 min after administration of the first dose of rhGH, leading us to review allergic and non-allergic skin reactions to rhGH. In our patient, an immediate skin reaction after administration of rhGH prompted a concern about a type I hypersensitivity reaction (HS) and the discontinuation of rhGH. However, after a dermatologic evaluation and observed administration of rhGH without subsequent rash, the initial eruption was likely an exacerbation of his underlying atopic dermatitis and a type I HS was felt to be unlikely. The rhGH was resumed and he has been on rhGH for the past 1 year with no recurrence of rash and with improvement in growth velocity.
Conclusions: Though rare, allergic and non-allergic skin reactions are known to occur with rhGH. It is important to know if the allergic reaction was due to the growth hormone molecule or one of the preservatives. It is also important to consider a non-allergic reaction due to flare up of underlying skin disorders as in our patient.

Keywords: allergic reaction to growth hormone; growth hormone therapy; hypersensitivity reaction to growth hormone.

Introduction

The development of recombinant hormones has allowed for improved treatment of many endocrine disorders. The most widely used recombinant hormones are insulin and growth hormone (GH). Other recombinant hormones include thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), parathyroid hormone (PTH) and insulin growth factor 1 (IGF1). Allergic reactions to these recombinant hormones are uncommon and have been widely studied particularly with regard to insulin due to its widespread use in treating diabetes. The incidence/prevalence of allergic reaction to recombinant insulin is <1–2.4% [1], with other recombinant hormones being reported at much lower rate.

Recombinant human growth hormone (rhGH) is widely used for growth related disorders [2]. The available rhGH preparations (Table 1) contain GH molecules, preservatives and buffers. Though development of immunoglobulin E (IgE) or immunoglobulin G (IgG) antibodies has been observed in some patients treated with rhGH [3, 4], clinical manifestation of an allergic reaction to rhGH is a rare side effect [4]. To date reported reactions, include local erythema, hives, generalized pruritus and urticaria [4–7]. The cause for allergic reaction to rhGH is either due

***Corresponding author: Bina Shah,** MD, Department of Pediatrics, Divisions of Pediatric Endocrinology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA, Phone: +(212) 562-3793, Fax: +(212) 562-3273, E-mail: bina.shah@nyumc.org
Shilpa Mehta, Patricia Zamora and Manish Raisingani: Department of Pediatrics, Division of Pediatric Endocrinology, New York University School of Medicine, New York, NY, USA
Vikash Oza: The Ronald O. Perelman Department of Dermatology, Division of Pediatric Dermatology, New York University School of Medicine, New York, NY, USA
Renee Potashner: Ruth and Bruce Rappaport School of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Table 1: Commonly used formulations of rhGH with preservative and buffer.

Brand name	Method of delivery	Preservative	Buffer
Genotropin	Pen with cartridge	m-Cresol	Phosphate
	Single dose syringe	No preservative	Phosphate
Humatrope	Vial	m-Cresol	Phosphate
Norditropin	Pre-loaded pen	Phenol	Histidine
Nutropin	Pen with cartridge	Phenol	Citrate
Omnitrope	Vial	Benzyl alcohol	Phosphate
	Pen with cartridge (5 mg)	Benzyl alcohol	Phosphate
	Pen with cartridge (10 mg)	Phenol	
Saizen	Vial	Benzyl alcohol	Phosphate
	Pen with cartridge	m-Cresol	Phosphate
Zomacton	Vial (5 mg)	Benzyl alcohol	No buffer
	Vial (10 mg)	m-Cresol	Phosphate
Accretropin	Vial	Phenol	Phosphate

rhGH, recombinant human growth hormone; m-Cresol, metacresol.

to be preservatives or the GH molecule itself. Allergic reactions to rhGH include immediate type IgE-mediated reactions and type III immune complex type [5, 7]. In addition to allergic reactions, exacerbation of pre-existing skin conditions has also been reported [8–12]. Despite its rarity, allergic reaction to GH is a significant clinical dilemma, because of its immediate side effects and its implication on continuation of GH treatment.

We report a case of a child with idiopathic short stature who developed a rash after the first dose of rhGH. The case prompted us to review the existing literature on allergic reactions to rhGH. Herein, we present the first review article focusing on allergic and non-allergic skin reactions caused by rhGH and discuss diagnostic and management options.

Case presentation

A 12-year-old healthy Hispanic boy with a history of atopic dermatitis presented with short stature. His height was 141 cm (<–2.28 SD) with a weight of 46 kg (0.61 SD) and a growth velocity of 2 cm/year. The mid-parental height was 165 cm. His physical examination revealed no dysmorphic features and Tanner stage 2 for pubic hair with testicular volume of 8 cc. A complete blood cell count, hepatic and renal function panel and urinalysis were within normal limits. Endocrine workup showed: free thyroxine (FT4), 1.22 ng/dL (0.9–1.9); TSH, 1.964 µIU/mL (0.9–4.2); IGF1, 132 ng/mL (146–541); insulin-like growth factor-binding protein 3 (IGFBP3), 2.5 mg/L (2.4–3.5); testosterone, 180.6 ng/dL (18–150); FSH, 7.4 U/L (1.6–8.0) and LH, 2.09 U/L (0.0–6.0). Bone age was 12 years for a chronological age of 12 years with a predicted adult height of 161 cm (–2.2 SD). GH stimulation test without priming with sex steroids showed a peak of 17.8 ng/mL. Magnetic resonance imaging (MRI) of the brain and pituitary was normal.

His past medical history was significant for mild atopic dermatitis with infrequent flares in limited to flexural area

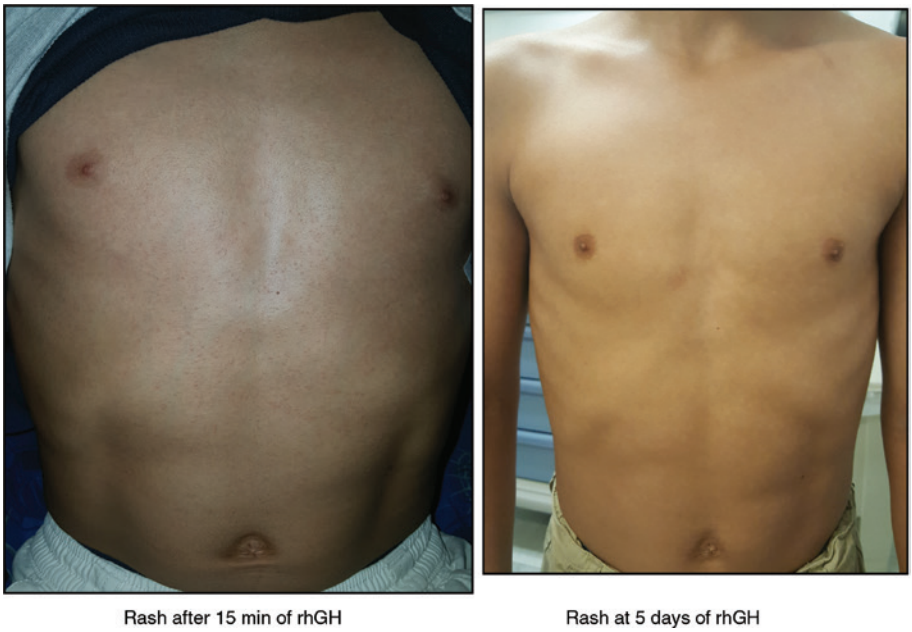

Figure 1: Pinpoint, skin colored papular rash after rhGH administration.

and not requiring prescription medications in the past 1 year. He had no known allergies to medications.

Based on his physical examination and laboratory workup, he was diagnosed with idiopathic short stature. The rhGH (Saizen® Serano) was prescribed at 0.27 mg/kg/week. He was given the first dose of rhGH 1.2 mg subcutaneously over the right thigh at home. His mother noted a rash after 15 min, consisting of pruritic papules localized to his chest and upper abdomen without a rash at the injection site (Figure 1). His pruritus subsided after application of 2.5% hydrocortisone ointment and an oral dose of benadryl. This rash gradually diminished and disappeared within 5 days. The rhGH was discontinued immediately out of concern for a possible allergic reaction. Further laboratory workup indicated a mild eosinophilia (6.1%) with a normal absolute eosinophil count (240) and the serum IgE, IgG were normal. Five days after the eruption, the patient was examined by a pediatric dermatologist and the physical exam revealed diffuse xerosis and scattered pinpoint, skin colored papules on the trunk felt to be most consistent with papular atopic dermatitis. The rest of his skin examination was normal. The patient was given his second dose rhGH (Saizen® Serano), 1.2 mg subcutaneously in the office and was supervised for 5 h. He did not develop a recurrence of this rash arguing against the likelihood that the reaction represented a type I hypersensitivity (HS) reaction. Our patient has remained on rhGH for the past 1 year with improved growth velocity and without side effects.

Discussion

GH was initially extracted from human cadaveric pituitary and used in the treatment of GH deficiency [13]. The transmission of Creutzfeldt-Jacob disease in some patients treated with human pituitary GH, as well as a dwindling supply, necessitated the development of a recombinant product [14, 15]. Recombinant hGH has been commercially available since 1985, approved for the use in various GH disorders [2, 16]. In the United States, rhGH is FDA-approved in GH deficiency [2] and other disorders of growth failure or short stature including Turner syndrome, chronic renal insufficiency before transplantation, Prader-Willi syndrome, a history of fetal growth restriction (small for gestational age [SGA], intrauterine growth retardation [IUGR]), short stature homeobox (SHOX) haploinsufficiency, Noonan syndrome and idiopathic short stature [17]. The rhGH is a polypeptide hormone of recombinant DNA origin, synthesized in a strain of *Escherichia coli*. It contains 191 amino acid residues, with an identical primary structure to human GH and a molecular weight of 22 kDa

Table 2: Allergic reaction to rhGH in hypopituitarism patients reported in the literature.

Author	rhGH	Age, years/ sex	Latency period, years	Time to reaction after rhGH	Reaction	Type HS	Skin test	Blood	Treatment
Walker et al. [5]	Humatrope	12/F	3	Immediate 30 min	– Hives at injection site – Generalized pruritic urticaria resolved with antihistaminic – Next injection with antihistaminic pretreatment – Generalized pruritic urticaria	I	+ Humatrope – m-Cresol		Desensitization Resume rhGH
Junprasert et al. [4]	Protropin	5/M	2.5	30 min	– Local erythema – Generalized pruritic urticaria	I	+ Protropin + Humatrope + Nutropin – B.W. – m-Cresol		Desensitization Resume rhGH
Forte et al. [7]	rhGH	12/F	None	2 weeks	– Hives on face and trunk – Arthralgia of right knee – Splenomegaly – Lymphadenopathy	III		+ Immune complexes to GH	rhGH contraindicated

rhGH, recombinant human growth hormone; HS, hypersensitivity; m-Cresol, metacresol; B.W., bacteriostatic water.

[18]. Most commercial formulations of rHGH (Table 1) include both a preservative and a buffer.

In this review, we focus on allergic and non-allergic skin reactions to rhGH. Though rare, allergic reactions to rhGH include immediate, type I IgE-mediated HS or type III immune-complex-mediated HS due to GH molecule itself (Table 2) [5, 7]. Type I IgE-mediated HS to rhGH was first reported by Walker et al. [5] in a 12-year-old female patient with hypopituitarism after 3 years of treatment with rhGH (humatrope) injection. Skin testing, pinprick and intradermal testing, was negative with metacresol (m-cresol) and benzyl alcohol alone, but had a wheal and flare reaction to diluted humatrope. Desensitization was performed using a series of subcutaneous injections of humatrope and treatment was resumed. Junaprasert et al. [4] reported type I IgE-mediated HS to rhGH (protropin). Skin test using protropin, humatrope and nutropin had a wheal and flare reaction, suggesting GH molecule being the culprit. Intravenous desensitization with humatrope was successful and treatment was resumed. Interestingly, later Forte et al. [7] reported a type III immune-complex-mediated HS with rhGH. The patient developed a maculopapular eruption with arthralgia, splenomegaly and lymphadenopathy. Immune complexes for GH molecule were found in peripheral blood by immunodiffusion technique, implicating that both the GH molecule and desensitization were contraindicated. We are unaware of a type IV or delayed type HS reaction occurring to GH molecule.

Beyond the molecule itself, preservatives used in rhGH can also be a source of adverse reactions. Common preservatives used in rhGH include benzyl alcohol, m-cresol or phenol. They are necessary to prevent microbial contamination of multi-use liquid products, particularly from opportunistic pathogens [19]. These preservatives are components in many other recombinant hormones including insulin where allergic reactions have been reported [20]. Theoretically, these inert preservatives can lead to either a type I, III or IV HS.

Benzyl alcohol is used commonly in many topical and diluent preparations as a solvent or preservative. Type I HS reactions to benzyl alcohol have rarely been reported [21]. In neonates, medications reconstituted with bacteriostatic water containing benzyl alcohol (>99 mg/kg/day) can result in gasping syndrome characterized by central nervous systemic depression, metabolic acidosis and gasping respirations [22, 23]. Due to a concern for this toxicity, neonates and infants are typically treated with preservative-free rhGH.

m-Cresol is a common preservative in both insulin and rhGH. Type I HS reactions to m-cresol have been reported with insulin [20, 24]. To our knowledge, only one case of m-cresol sensitivity associated with rhGH has been reported. The patient developed extreme tenderness at the injection site and myositis, which was resolved by replacing m-cresol with sterile water. It is possible that change of rhGH preparation with an alternative preservative is underreported.

Phenol has been successfully used as a preservative in drug formulations for more than 50 years and is considered a safe and effective agent which complies with strict international requirements for preservatives in drug formulations [19]. To our knowledge, no cases of sensitivity to phenol when used as a preservative in rhGH have been reported in the literature. Clinicians should have a working knowledge of the preservatives contained in rhGH as switching to rhGH with a different preservative may be important in managing patients with presumed allergic reactions to rhGH [25].

Common buffers used in rhGH formulations include phosphates, carbonates, histidine and citrate. Buffers are used in these formulations to regulate the pH of the solution [19]. To our knowledge, they are reported to cause pain at the local injection site but not allergic reactions [26].

The mechanism involved in allergic skin reactions with rhGH is either a type I or type III HS reaction. Type I HS due to rhGH is an IgE-mediated response that occurs immediately within 30 min after injection. Local symptoms typically present immediately after rhGH injection and include injection site swelling erythema and itching. The reaction may become generalized presenting with urticaria, angioedema and even anaphylaxis. Treatment is to stop the inciting agent immediately. Desensitization may be helpful [4, 5]. Type III HS due to rhGH is mediated by immune complex deposition. These reactions are usually of delayed onset occurring days to weeks later. It can manifest as a local Arthus reaction with the development of subdermal tender nodules at the injection site. In rare cases, a serum-sickness-like reaction to the drug where an immune-complex-medicated vasculitis results in inflammation of the skin, joints, kidney and other organs. In this scenario, treatment involves stopping the inciting agent and desensitization is contraindicated [7]. Type IV HS can develop to preservatives used in rhGH and can present as itching and dermatitis at an injection site or very rarely as a generalized eczematous eruption. Patch testing can be used to confirm whether a preservative is a source of type IV reaction [21].

The rhGH may also cause non-allergic skin reactions by exacerbation of underlying skin conditions. Lichenoid skin reactions have been reported with the use of rhGH (Table 3) [8, 9]. Oono and Arata [9] reported on the exacerbation of lichen planus in a 9-year-old female

Table 3: Non-allergic reaction to rhGH: exacerbation of underlying skin disease.

Author	Age, years/ sex	Diagnosis	Latency period, months	Reaction	Treatment for skin condition	Impact of rhGH on skin condition
Oono and Arata [9]	9/M	GHD	1	Flat-topped papules plaques of lichen planus	Unresponsive to topical steroid	Improvement with D/C rhGH
Soares and Mendonca [8]	9/F	TS	1	Scaly papules on skin and keratotic lines of labial and buccal mucosa due to lichen planus-like drug reaction	Partial improvement with topical steroid	Improvement with D/C rhGH
Maghnie et al. [12]	9.5/F	GHD	N/A	Psoriasiform lesions	Unresponsive to topical steroid	Improvement with D/C rhGH
Pirgon et al. [11]	8/M	GHD	6	Psoriasiform lesions	Partial improvement with topical steroid and clemastine	Improvement with reduction of rhGH
Acikgoz et al. [10]	12/F	TS	3	Psoriasiform lesions	Resolution with topical calcipotriol	Continuation of rhGH

rhGH, recombinant human growth hormone; GHD, growth hormone deficiency; TS, Turner syndrome; D/C, discontinuation.

with hypopituitarism. The patient's lichen planus did not respond to potent topical steroids, but improved with discontinuation of rhGH [9]. Soares and Mendonca [8] reported a case of a lichenoid drug eruption in a 9-year-old female with Turner syndrome which improved with discontinuation of rhGH. Exacerbations of psoriasis have also been reported with rhGH treatment [11, 12]. Maghnie et al. [12] reported a 9.5-year-old girl with hypopituitarism and chronic, plaque-stage psoriasis who developed acute exacerbations of psoriasis after GH treatment which subsequently resolved upon discontinuation. Pirgon et al. [11] reported the development of psoriasiform lesions in a previously unaffected, 8-year-old child with hypopituitarism after rhGH treatment.

The mechanism by which rhGH replacement therapy could exacerbate an underlying dermatologic disorder such as atopic dermatitis, lichen planus or psoriasis is not fully known. The exacerbation may be noticed immediately as in our patient or be delayed by 1–6 months or longer (Table 3). Proposed mechanisms include stimulation of the GH receptor (GHR) in the skin [10] or perturbation of the underlying immune pathogenesis of the condition [8]. The GHR and IGF1 receptors are found in both epidermis and dermis [27–29]. Higher IGF1 expression is seen in proliferating keratinocytes explaining in part rare cases of psoriasis exacerbation [30]. Therefore, rhGH replacement therapy could theoretically stimulate increased IGF1 production and hence increase keratinocyte cell turnover.

GH is purported to modulate both the humoral and cellular arms of the immune system and therefore replacement therapy could have a theoretical role in altering the immunologic basis of some skin disorders [31]. In vitro studies have shown that treatment of cells of the immune system with GH can lead to increased immunoglobulin secretion of B cells, thymulin secretion of thymic epithelial cells, natural killer (NK) cell activity, phagocytosis, oxidative burst and killing capacity of neutrophils and macrophages [32, 33]. Recent study also reported lymphocyte migration, including developing and mature cells, can be modulated by GH [34].

In our patient, the flare up of his atopic dermatitis shortly after his first injection of rHGH may have only been coincidental as atopic dermatitis normally has a relapsing and remitting course. However, given GH's role in both keratinocyte proliferation and immune function, the temporal correlation of the flare with rhGH could also reflect the broad functions of this hormone.

Evaluation and management of possible rhGH allergy (Figure 2)

Initial evaluation of a rhGH allergy involves determining whether a cutaneous eruption is a HS reaction or an exacerbation of a pre-existing dermatologic condition. Dermatologic consultation may be helpful in characterizing the morphology of the rash. If a type I HS is suspected, skin prick testing and allergy specific serum IgE titers can be useful in further confirming a diagnosis. If type III HS is suspected, serum specific IgG to rhGH (anti GH antibodies) and immune complex titers to GH molecule by the immunodiffusion procedure (commercially not available)

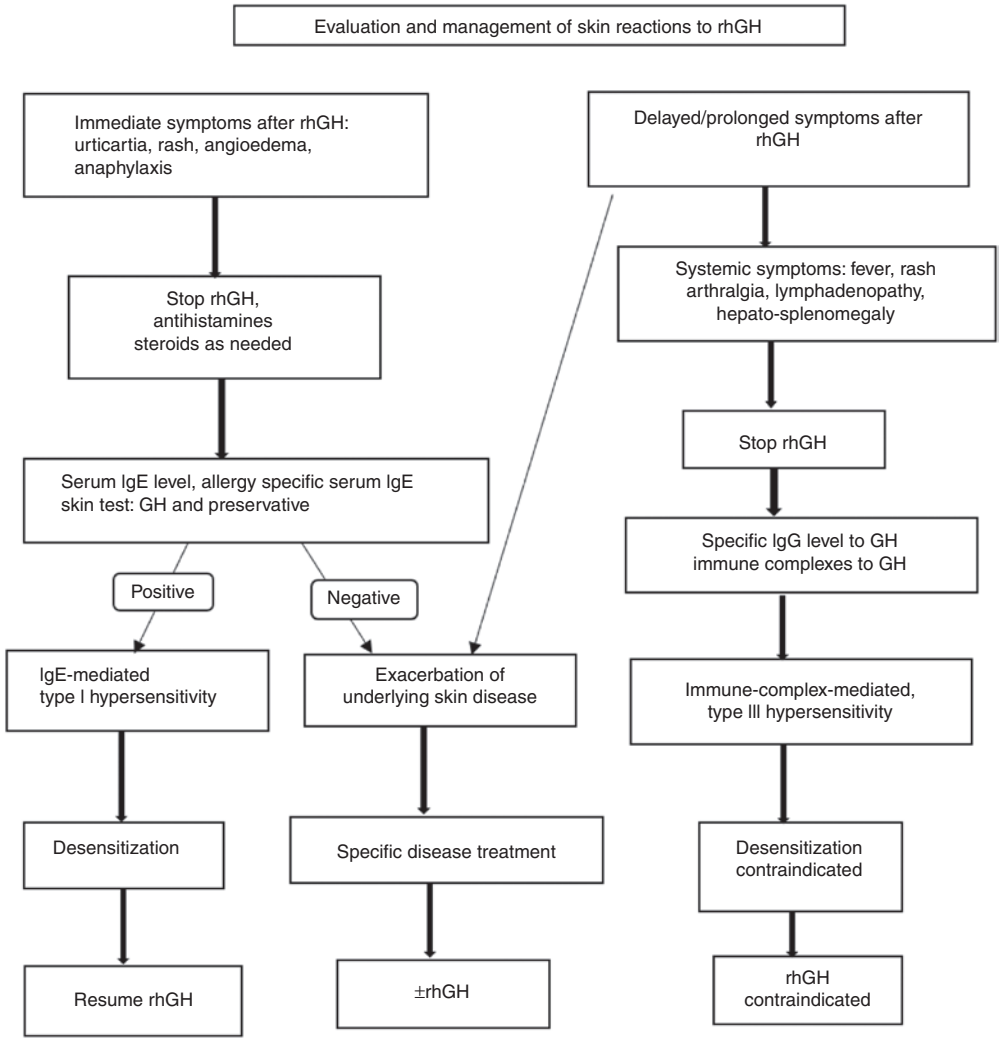

Figure 2: A diagnostic algorithm for patients suspected of having an rhGH allergy.
rhGH, recombinant human growth hormone; GH, growth hormone.

can be pursued. A key step in the investigation of rhGH HS is to determine whether the reaction is due to the GH molecule itself or a preservative. When a sensitization is due to a preservative, the allergen can be avoided by choosing an alternative preparation of rhGH (Table 1). Patch testing may be particularly useful if the complaint is persistent itching and/or dermatitis at an injection site. In type I HS to GH molecules, desensitization techniques can be considered [4, 5]. If proved to be type III HS, desensitization is contraindicated and the patient cannot resume rhGH treatment. If type I HS is ruled out and history is suggestive of underlying skin disease, exacerbation of skin disease should be considered. This can be managed with specific disease treatment. If there is no improvement in skin disease, then discontinuation of rhGH should be considered. In our patient, after ruling out type I HS reaction, we restarted rhGH under supervised setting without further exacerbation of his underlying atopic dermatitis.

In conclusion, allergic and non-allergic skin reactions are known to occur with rhGH. It is important to identify whether the cause of the allergic reaction was GH molecule or preservatives. In addition, a non-allergic reaction due to flare up of underlying skin disorders should be considered.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Wonders J, Eekhoff EM, Heine R, Bruynzeel DP, Rustemeyer T. Insulin allergy: background, diagnosis and treatment [in Dutch]. Ned Tijdschr Geneeskd 2005;149:2783–8.
2. Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016;86:361–97.
3. Petersen KG, Khalaf A, Zeisel HJ, Stryjek-Kaminska D, Kerp L. IgE antibodies to human growth hormone prior to and during treatment. Acta Endocrinol 1989;121:501–4.
4. Junprasert J, Javier FC, 3rd, Rodriguez JA, Moore C, Sorensen RU. Successful intravenous desensitization of growth hormone hypersensitivity. J Pediatr Endocrinol Metab 1997;10:223–6.
5. Walker SB, Weiss ME, Tattoni DS. Systemic reaction to human growth hormone treated with acute desensitization. Pediatrics 1992;90(1 Pt 1):108–9.
6. Albertsson-Wikland K. Clinical trial with authentic recombinant somatropin in Sweden and Finland. Acta Paediatr Scand Suppl 1987;331:28–34.
7. Forte WC, Kochi C, Faria CD, Calliari LE, Monte O, et al. [Growth hormone therapy and hypersensitivity type III reaction: a contraindication for desensitization]. Arq Bras Endocrinol Metabol 2011;55:78–80.
8. Soares MQ, Mendonca EF. Lichen planus-like drug reaction associated with recombinant human growth hormone therapy in a child patient with Turner syndrome. Dermatol Online J 2016;22:14.
9. Oono T, Arata J. Childhood lichen planus in a patient receiving growth hormone for dwarfism. Dermatology 1996;192:87–8.
10. Acikgoz G, Ozmen I, Tunca M, Akar A, Arca E, et al. Psoriasis induced by growth hormone therapy in a patient with Turner's syndrome. Int J Dermatol 2015;54:e132–5.
11. Pirgon O, Atabek ME, Sert A. Psoriasis following growth hormone therapy in a child. Ann Pharmacother 2007;41:157–60.
12. Maghnie M, Borroni G, Larizza D, Lorini R, Girani MA, et al. Relapsing eruptive psoriasis and immunological changes triggered by growth hormone therapy in a growth hormone-deficient girl. Dermatologica 1990;181:139–41.
13. Li CH, Papkoff H. Preparation and properties of growth hormone from human and monkey pituitary glands. Science 1956;124:1293–4.
14. Degenerative neurologic disease in patients formerly treated with human growth hormone. Report of the Committee on Growth Hormone Use of the Lawson Wilkins Pediatric Endocrine Society, May 1985. J Pediatr 1985;107:10–2.
15. Ayyar VS. History of growth hormone therapy. Indian J Endocrinol Metab 2011;15(Suppl 3):S162–5.
16. Lindholm J. Growth hormone: historical notes. Pituitary 2006;9:5–10.
17. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003;143:415–21.
18. Rezaei M, Zarkesh-Esfahani SH. Optimization of production of recombinant human growth hormone in Escherichia coli. J Res Med Sci 2012;17:681–5.
19. Kappelgaard AM, Bojesen A, Skydsgaard K, Sjogren I, Laursen T. Liquid growth hormone: preservatives and buffers. Horm Res 2004;62(Suppl 3):98–103.
20. Ghazavi MK, Johnston GA. Insulin allergy. Clin Dermatol 2011;29:300–5.
21. Fisher AA. Allergic paraben and benzyl alcohol hypersensitivity relationship of the "delayed" and "immediate" varieties. Contact Dermatitis 1975;1:281–4.
22. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 1982;307:1384–8.
23. Lovejoy FH, Jr. Fatal benzyl alcohol poisoning in neonatal intensive care units. A new concern for pediatricians. Am J Dis Child 1982;136:974–5.
24. Rajpar SF, Foulds IS, Abdullah A, Maheshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. Contact Dermatitis 2006;55:119–20.
25. Bach MA, Blum DM, Rose SR, Charnas LR. Myalgia and elevated creatine kinase activity associated with subcutaneous injections of diluent. J Pediatr 1992;121:650–1.
26. Yu AW, Leung CB, Li PK, Lui SF, Lai KN. Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alpha. Int J Artif Organs 1998;21:341–3.
27. Oakes SR, Haynes KM, Waters MJ, Herington AC, Werther GA. Demonstration and localization of growth hormone receptor in human skin and skin fibroblasts. J Clin Endocrinol Metab 1992;75:1368–73.
28. Thorsson AV, Hintz RL, Enberg G, Hall K. Characterization of insulin-like growth factor II binding to human fibroblast monolayer cultures. J Clin Endocrinol Metab 1985;60:387–91.
29. Nissley SP, Rechler MM. Somatomedin/insulin-like growth factor tissue receptors. Clin Endocrinol Metab 1984;13:43–67.
30. Edmondson SR, Thumiger SP, Werther GA, Wraight CJ. Epidermal homeostasis: the role of the growth hormone and insulin-like growth factor systems. Endocr Rev 2003;24:737–64.
31. Kelley KW, Weigent DA, Kooijman R. Protein hormones and immunity. Brain Behav Immun 2007;21:384–92.
32. Weigent DA. Immunoregulatory properties of growth hormone and prolactin. Pharmacol Ther 1996;69:237–57.
33. Kooijman R, Hooghe-Peters EL, Hooghe R. Prolactin, growth hormone, and insulin-like growth factor-I in the immune system. Adv Immunol 1996;63:377–454.
34. Smaniotto S, Martins-Neto AA, Dardenne M, Savino W. Growth hormone is a modulator of lymphocyte migration. Neuroimmunomodulation 2011;18:309–13.