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Successful desensitization to gonadotropin-releasing hormone analogue triptorelin acetate using a sustained-release depot preparation

To the Editor,

Gonadotropin-releasing hormone (GnRH) analogues are commonly used in pediatric patients in the treatment of central precocious puberty.¹ GnRH analogues suppress the secretion of gonadotropins and sex hormones, preventing progression to advanced puberty and reduced final adult height secondary to accelerated fusion of growth plates. GnRH analogues are also used in adults for treatment of endometriosis² and prostatic cancer.³ Hypersensitivity reactions to GnRH analogues are exceedingly rare,⁴⁻⁶ and to date, we are unaware of any desensitization protocols for GnRH hypersensitivity in the literature or used in clinical practice.

Our patient is a 6-year-old girl who was first diagnosed with idiopathic central precocious puberty at age 5 years and 4 months when she presented with bilateral breast buds. She was commenced on monthly depot injections of Triptorelin, a GnRH analogue, to arrest further progression into advanced puberty.

She had first been given an intramuscular (IM) injection of triptorelin embonate depot but experienced excessive pain at the injection site which is a known side effect. She was therefore switched to IM triptorelin acetate depot, a different formulation of Triptorelin, in the second month of her treatment. However, she developed generalized urticaria an hour after her second dose of IM triptorelin

FIGURE 1 Immediate-type hypersensitivity reaction to triptorelin acetate. The patient developed generalized urticaria an hour following administration of her second dose of IM triptorelin acetate [Colour figure can be viewed at wileyonlinelibrary.com]



TABLE 1 Triptorelin acetate desensitization protocol

Monthly triptorelin acetate injection	Pre-medication		Triptorelin acetate dose	
	Night before injection	30 min before injection		
#1	PO prednisolone + cetirizine	PO prednisolone + cetirizine	Half dose	Post-injection monitoring for allergic reactions should be performed within a medical facility equipped with staff and medications to manage potential allergic reactions. A monitoring duration of 4 h is recommended. Ensure that patient has an anaphylaxis action plan, functional adrenaline auto-injector, and antihistamines prior to discharge.
#2	PO prednisolone + cetirizine	PO prednisolone + cetirizine	Full dose	
#3	PO cetirizine	PO prednisolone + cetirizine	Full dose	
#4	PO cetirizine	PO cetirizine	Full dose	
#5 and subsequent injections	—	PO cetirizine	Full dose	

Suggested protocol for a pediatric patient with triptorelin acetate hypersensitivity. Suggested dose of PO prednisolone is 1 mg/kg/dose (maximum dose: 40 mg). PO Cetirizine doses are as follows: <2 years: 2.5 mg; 2–5 years: 5 mg; > 5 years: 10 mg).

acetate (Figure 1). This resolved with one dose of per oral (PO) antihistamine. She did not have any other systemic symptoms and her vital signs remained stable. Subsequently, an open drug challenge was again positive, as she again developed generalized urticaria 1.5 hours after the administration of IM triptorelin acetate, which confirmed the diagnosis of an immediate-type hypersensitivity reaction.

As there were no alternative GnRH analogues available in Singapore, where this patient lives, a referral was made to an allergy specialist and a 5-step desensitization regimen to depot triptorelin acetate was designed (Table 1) to allow her to continue receiving optimal medical therapy safely.

The patient received PO prednisolone and PO cetirizine the night before and 30 minutes before the first visit. For the first step in the protocol, half the target dose of IM triptorelin acetate was administered. She was monitored uneventfully for 4 hours in the outpatient Day Therapy Centre located within our tertiary hospital. She was discharged well, with an adrenaline auto-injector, PO cetirizine, and anaphylaxis action plan as a precautionary measure.

Monthly IM triptorelin acetate depots were subsequently administered with tapering doses of pre-medications as outlined in Table 1. She reported episodes of mild, intermittent urticaria 2–3 weeks after

each injection. These episodes were consistent with breakthrough reactions that can be expected to occur in the early phases of desensitization.⁷ The timeline for occurrence of these reactions was consistent with the delayed release of the depot and was easily managed with antihistamines. The intensity and frequency of urticaria decreased with each step of the desensitization protocol and resolved completely from the 8th triptorelin acetate injection onwards. She now continues to receive monthly IM triptorelin acetate doses with PO cetirizine as a single pre-medication 30 minutes before each injection without further reactions.

Skin prick (SPT) and intradermal (IDT) tests were performed on the day of the 6th step of the desensitization protocol due to patient-related constraints, as discussed later. Undiluted triptorelin acetate solution (172 mg/mL) was used with appropriate positive and negative controls. This concentration was also found to be non-irritating on two healthy control subjects. SPT was equivocal (wheal 2 mm), and the IDT showed a significant flare reaction but no significant increase in wheal size [0 min: erythema 4 × 4 mm, wheal 4 × 4 mm; 15 minutes: erythema 15 × 15 mm, wheal 4 × 4 mm].

This is the first reported desensitization regime for a patient with hypersensitivity to triptorelin acetate—a GnRH analogue administered in a slow-release depot form. A starting dose of half the

therapeutic dose was chosen based on the following reasons: Firstly, this formulation comprises triptorelin acetate molecules coupled to microspheres of a biodegradable polymer. The active drug is reconstituted by mixing the lyophilized powder in its buffer solution, which solidifies rapidly into a semi-solid gel which is then administered as a depot injection. The rapid solidification process made it logistically impossible to further dilute the drug into smaller volumes.

Secondly, after IM administration, an immediate release of triptorelin acetate occurs, resulting in the first peak in drug levels on day 1, followed by a slower sustained release from day 4 onwards. Around 38% of the injected Triptorelin is released during the first 13 days and 0.9% daily thereafter.⁷ The drug's unique pharmacokinetics require deviation from the existing rapid desensitization protocols designed for PO or IV medications with immediate release pharmacokinetics, which generally begin with a starting dose of 1/10 000 to 1/100 of the target dose with stepwise dose increments in a single rapid desensitization setting.⁸ This approach also obviates the need for repeated IM injections within a short timeframe, which would not be tolerated by a young child. The slow sustained release of triptorelin acetate, administered intramuscularly in depot form, enhances the efficacy and safety of the desensitization process compared to drugs administered via the PO or IV route which are quickly absorbed and attain high blood concentrations soon after administration.

Thirdly, there was an urgent need to halt the progression of precocious puberty which can only be achieved by monthly therapeutic doses of triptorelin acetate. Following generally accepted protocols, beginning with low starting doses and slow stepwise increments would result in a delay in achieving therapeutic doses of triptorelin acetate and timely suppression of pubertal progression. Prolonged administration of low doses of GnRH agonists (triptorelin acetate) may instead upregulate GnRH receptors, stimulating further progression of puberty.⁹

The use of pre-medications routinely in drug desensitization remains debatable. Of the various types of pre-medications, antihistamines are most common. It has been recommended that other pre-medications, such as corticosteroids, may be added if the prior allergic reactions were clinically significant.¹⁰ The decision to use both an antihistamine and a corticosteroid in our protocol was based on the premise that the patient's risk of developing a reaction was high, given that the starting dose was higher than those used in conventional rapid desensitization protocols. The corticosteroid doses were however reduced quickly with each step of the protocol and stopped completely from the 4th step onwards.

Limitations include the lack of pre-desensitization skin prick, intradermal, and basophil activation tests. These could not be performed prior to the desensitization protocol due to the patient's pre-medication regimen, the family's financial constraints which precluded the use of a separate triptorelin acetate vial for skin testing, as well as their preference not to return to the hospital in between the desensitization doses for further work up. Performing the skin tests after commencement of desensitization may have reduced the magnitude of the skin reactions, hence yielding an equivocal SPT and an IDT with significant flare reaction but no significant increase in wheal size.

Furthermore, including a lower drug dilution to IDT would have been useful in differentiating between a true immune-mediated reaction versus an irritative reaction. Unfortunately, the rapid solidification of triptorelin acetate and lack of a suitable alternative diluent compatible with the microspheres precluded further dilution. Based on these limitations, we relied on the skin test results on two healthy controls to infer a non-irritating drug concentration for triptorelin acetate.

In summary, hypersensitivity reactions to GnRH analogues are rare but can nevertheless be potentially life-threatening.⁴⁻⁶ Switching to an alternative GnRH analogue still carries a small risk of cross-reactivity.^{4,5} This novel desensitization protocol allowed for the continued safe use of triptorelin acetate, an essential therapeutic agent for idiopathic central precocious puberty, in a setting where no alternative therapeutic options were available.

We demonstrate a unique approach to desensitization using a sustained-release depot preparation along with pre-medications. This approach harnesses the advantages of the drug's pharmacokinetics which achieve slow delivery of the drug throughout the month, which maintains a stable concentration of the drug in the system. This effectively replicates the slow escalation approaches of other conventional drug desensitization protocols. Thus, it may be reasonable to speculate that this distinctive feature makes sustained-release depot preparations an ideal candidate for safe and successful desensitization and that the approach adopted in our protocol may be generalizable to other depot delivery drug hypersensitivities as well.

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CONFLICT OF INTEREST

The authors do not have any conflict of interests to declare.

CLINICAL IMPLICATIONS

Safe and effective desensitization with IM triptorelin acetate depot can be achieved with a standardized protocol.

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The importance of functional validation after next-generation sequencing: evaluation of a novel *CARD11* variant

To the Editor:

The advent of next-generation sequencing (NGS) techniques such as whole exome sequencing (WES) has greatly accelerated the identification and treatment of rare Mendelian diseases. In particular, these approaches have demonstrated immense utility for identifying inborn errors of immunity (primary immunodeficiencies [PIDs]). This impact is emphasized by the fact that of the estimated 350 gene defects linked to inborn errors of immunity, ~100 have been described since the implementation of NGS techniques in 2010.¹

Within the broad spectrum of inborn errors of immunity, the combined immunodeficiency disorders (CIDs) are caused by a group of gene defects that result in dysfunctional lymphocyte activation. Nuclear factor- κ B (NF- κ B) is a central regulator of lymphocyte activation, proliferation, and differentiation. Its activation is facilitated by the assembly of the caspase recruitment domain family member 11 (CARD11)—B-cell CLL/lymphoma 10 (BCL10)—MALT1 paracaspase (MALT1) (CBM) signalosome.² Confirming the critical role of the CBM complex in immunity, patients have now been identified with mutations in each of the three CBM components, resulting in a unifying

phenotype of aberrant NF- κ B activation, abnormal T- and B-cell development and function, and recurrent infections.² CARD11 is unique in the range of “CARD11-opathies” that are caused by the three categories of germline mutations identified in this gene: (i) homozygous loss-of-function mutations causing combined immunodeficiency³; (ii) heterozygous gain-of-function mutations leading to “B cell expansion with NF- κ B and T cell anergy” (BENTA) disease⁴; and (iii) heterozygous CARD11 mutations with dominant-interfering activity resulting in severe atopic disease.⁵ Here, we report the functional impact of a homozygous CARD11 variant (c.1798G>T, p.D600Y).

The index patient is an 11-year-old Canadian First Nations boy born to unrelated parents. Immediate family history was unremarkable, with the exception of his mother, who was diagnosed with rheumatoid arthritis at age 21. His two younger sisters and one younger brother are all reported to be healthy, while an older brother died from an accidental injury (Figure 1A). Infectious history was notable for several episodes of oral candidiasis until age 2 years, an episode of pneumonia requiring hospitalization, and a prolonged episode of diarrhea positive for *Cryptosporidium* spp. He suffered