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An approach to natalizumab hypersensitivity: a case series of induction of tolerance

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Abstract

Induction of tolerance protocols have been applied successfully to manage allergic reactions to many medications. Hypersensitivity reactions to natalizumab (TYSABRI®) have been recognized as a growing problem. In circumstances where a hypersensitivity reaction to a medication has occurred, but no suitable alternative exists, drug induction of tolerance protocols may be considered. Drug induction of tolerance protocols were performed in three patients with prior hypersensitivity reactions to natalizumab. All three patients tolerated the protocol without adverse reactions, allowing for the safe reintroduction of natalizumab. To conclude, this case series demonstrates success with an induction of tolerance procedure to a highly effective biological agent for multiple sclerosis, in patients with allergic reactions to natalizumab.

Keywords

immunology, multiple sclerosis, natalizumab, relapsing–remitting, tysabri

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Introduction

Induction of tolerance protocols have been applied successfully for many different medications, including antibiotics, chemotherapeutics and biologics.^{1,2,3} Natalizumab (TYSABRI®) is a humanized monoclonal antibody against the cellular adhesion molecule alpha-4 integrin, indicated for the treatment of relapsing–remitting multiple sclerosis (RRMS) and Crohn's Disease. Hypersensitivity reactions to natalizumab are a growing dilemma,^{4,5,6} and adverse events described in the literature vary from urticaria and anaphylaxis, to delayed maculopapular eruptions. The AFFIRM trial described hypersensitivity reactions in 4% of patients during or within 1 hour after the infusion.^{7,8} Calabresi and colleagues noted the presence of neutralizing anti-natalizumab antibodies in patients with type I hypersensitivity reactions after several infusions.⁸ We report three patients with RRMS in whom prior hypersensitivity reactions to natalizumab occurred, who requested induction of tolerance to this monoclonal antibody.

Hypersensitivity reactions and infusion reactions

The Gell and Coombs classification system is the most commonly used method for describing drug hypersensitivity reactions, which are by definition immunologic in nature.⁹ Type I hypersensitivity reactions are immediate in onset resulting from the presence of drug-specific IgE antibodies, and can present with urticaria and angioedema, to anaphylaxis. Type II cytotoxic

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reactions are mediated by drug-specific IgG or IgM antibodies, whereas type III reactions are mediated by immune complex deposition and present with serum sickness or serum-sickness like reactions. Lastly, type IV reactions, or cellular-mediated reactions, are delayed and often present with maculopapular eruptions. The development of Stevens–Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) are also cell-mediated, but are life-threatening hypersensitivity reactions that preclude reintroduction of the offending medication.

Induction of drug tolerance

In circumstances where a hypersensitivity reaction to a medication has occurred, but no suitable alternative exists, drug induction of tolerance protocols may be considered.³ ‘Drug desensitization’ alters one’s immune response to a medication, allowing temporary tolerance for the duration of exposure.⁹ Desensitization only applies to type I hypersensitivity reactions, as these patients have been ‘sensitized’ with production of drug-specific IgE antibodies. However, similar protocols have been developed for non-IgE mediated reactions, where patients may not have been truly sensitized to a medication. Therefore, the term ‘drug induction of tolerance’ is more widely accepted, encompassing protocols that combat both IgE and non-IgE-mediated hypersensitivity reactions.⁹

Drug tolerance describes a temporary alteration in the immune mechanisms of drug allergy, thereby allowing the safe administration of a specific medication.⁹

In order to maintain this temporary state of tolerance, the patient must continue to receive the medication regularly. For medications that are dosed frequently, such as antibiotics, daily administration maintains this state of tolerance. This poses a dilemma for once monthly chemotherapeutics and biologics, as the dosing interval may result in resensitization. Thus, with biologics and chemotherapeutics, the procedure or a modified version of the procedure must be repeated with each dose.

Case descriptions

Table 1 summarizes three different case reports, each describing patients with RRMS who developed hypersensitivity reactions to natalizumab.

Methods

The developed protocol involves a pretreatment regimen followed by stepwise increasing concentrations of natalizumab. Our protocol (Figure 1) utilizes the induction of a tolerance regimen developed by Castells et al.¹ All staff involved were certified by the TOUCHTM Prescribing Program to administer natalizumab. The risks and benefits of induction of tolerance were discussed in detail with each patient, and informed consent was obtained. The initial protocol was performed in our allergy office with one-to-one nursing staff equipped to manage anaphylactic reactions. Subsequent infusions were performed in their neurologist’s infusion center, provided their nursing staff felt comfortable recognizing and managing allergic reactions.

Table 1. Comparison of patients

	Patient 1	Patient 2	Patient 3
Age (years)	22	25	54
Gender	Female	Female	Female
Duration of disease	3 years	4 years	4 years
Prior therapies	Glatiramer, Corticosteroids	Interferon beta-1b, IVIG	Glatiramer
Symptoms of reaction	Urticaria, Shortness of breath, Intractable cough, brief in duration	Flushing during infusion, Diffuse urticaria the following day, continued for 2 weeks	Flushing and urticaria during infusion, brief duration
Timing of reaction	With 2nd infusion	With 1st infusion	After 26th infusion
Skin prick testing with natalizumab (20mg/ml)	Negative	Borderline positive	Negative
Presence of anti-natalizumab IgG antibodies	Negative	Negative	Negative
Gell and Coombs hypersensitivity reaction	Type I ^a	Type I ^a /Type III ^b	Type I ^a

^aIgE-mediated, immediate hypersensitivity reaction

^bMediated by deposition of immune complexes (e.g. serum sickness)

STEP 1: Mixing of 3 solutions. Start by mixing the most concentrated bag (Solution 3), followed by 1:10 fold dilutions of each solution as instructed below.					
Solution No.	Solution mixture			Solution final concentration	
Solution 3	300mg of natalizumab added to 100ml of normal saline			3mg/ml	
Solution 2	10ml of solution 3 added to 90ml of normal saline			0.3mg/ml	
Solution 1	10ml of solution 2 added to 90ml of normal saline			0.03mg/ml	
STEP 2:					
Premedications:					
Patient 1: Prednisone 60mg per day x 3 days (the day prior, the day of, the day following infusion); Diphenhydramine 50mg PO, 30 minutes prior to infusion; Alprazolam (Xanax®) 0.5mg PO, 30 minutes prior to infusion					
Patients 2 and 3: Prednisone 60mg per day x 3 days (the day prior, the day of, the day following infusion); Diphenhydramine 50mg PO, 30minutes prior					
STEP 3:					
Infusion of each solution using the below protocol, starting with the most dilute bag (Solution 1) and finishing with the most concentrated (Solution 3). Rate of infusion is doubled after 15minute time intervals, to a maximum rate of 160ml/hr until the bag is complete. Vital signs are assessed prior to each rate change, and prior to changing solutions.					
Solution 1 (0.03mg/ml natalizumab)					
Step No.	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
1	10	15	2.5	0.075	0.075
2	20	15	5	0.15	0.225
3	40	15	10	0.3	0.525
4	80	15	20	0.6	1.125
5	160	23.4	62.5	1.875	3
Solution 2 (0.3mg/ml natalizumab)					
Step No.	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
6	10	15	2.5	0.75	3.75
7	20	15	5	1.5	5.25
8	40	15	10	3	8.25
9	80	15	20	6	14.25
10	160	19.7	52.5	15.75	30
Solution 3 (3mg/ml natalizumab)					
Step No.	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Administered dose (mg)	Cumulative dose (mg)
11	10	15	2.5	7.5	37.5
12	20	15	5	15	52.5
13	40	15	10	30	82.5
14	80	15	20	60	142.5
15	160	19.7	52.5	157.5	300
Total time ~4 hours					

Figure 1. Initial natalizumab induction of tolerance.

Results

All three patients tolerated the initial induction of tolerance without any serious adverse events. Patient 1 experienced anxiety prior to the procedure, necessitating the use of a benzodiazepine as a premedication. She tolerated a subsequent infusion, but later discontinued further treatment secondary to her continued anxiety.

Patient 2 has received a total of 12 infusions without any adverse reactions. An abbreviated protocol, or modified induction of tolerance, was developed for subsequent infusions to be performed at her neurologist's office. Patient 3 developed mild flushing to the neck and chest during step 4 of her infusion, which resolved with diphenhydramine; she received the remainder of solution 1 at a lower rate without further reactions.

Five subsequent infusions were successfully administered at her neurologist's infusion center, also utilizing the modified induction of tolerance protocol.

Discussion

This case series is the first to report successful induction of tolerance to natalizumab. Although the exact mechanisms behind induction of tolerance are not fully understood, these protocols are utilized in the setting of drug hypersensitivity reactions with significant success.^{1,2} As a temporary state of tolerance is induced, the interval period with once monthly chemotherapeutics and biologics may result in resensitization to the medication. Thus, with natalizumab, a modified induction of tolerance procedure was repeated with each dose.

As presented in each case description, the type of hypersensitivity reaction was deduced based on the history, despite skin testing results. Skin testing for drug allergy detects the presence of specific IgE antibodies to a medication. However, IgE is produced against the medication's immunogenic epitopes, which may not be present in its intact form and may only be displayed on its metabolites or determinants. These specific determinants are antigenic in nature, thus stimulating the production of drug-specific IgE. Therefore, skin testing may be negative even with type I hypersensitivity reactions, as testing is often performed with the unmetabolized medication, and not its antigenic determinants.

As neutralizing anti-NTZ antibodies have been shown to decrease natalizumab's clinical efficacy,⁸ such patients may not be suitable candidates for induction of tolerance. As Calabresi and colleagues found an association between type I hypersensitivity reactions and anti-NTZ IgG,⁸ assessing for the presence of these neutralizing antibodies may be warranted in such cases. It is unclear whether induction of tolerance would be successful in these patients, and if the presence of blocking antibodies would impede the production of tolerance. Nonetheless, as anti-NTZ antibodies were not detected in our three patients, we felt they were suitable candidates for this protocol.

In patients with chronic medical conditions that are resistant to multiple treatment regimens, the development of hypersensitivity reactions to alternative therapeutics can be severely limiting. Choosing an alternative medication should always be considered when facing drug induced hypersensitivity reactions; however, in patients who have failed to respond to alternatives, induction of tolerance may be pursued.

Drug induction of tolerance procedures allow patients the option of continuing on such medications, especially if other treatment regimens have failed. This case series demonstrates success with an induction of tolerance procedure to a highly effective biological agent for multiple sclerosis, in patients with allergic reactions to natalizumab.

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Conflict of interest statement

None declared.

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