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Fontos gyógyszerbiztonsági információ

A Norditropin NordiFlex (szomatropin, humán növekedési hormon) készlethiány miatt a betegek átállítása más alternatív készítményekre

Tisztelt Doktornő / Doktor Úr!

A Novo Nordisk A/S az Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézettel (OGYÉI) egyetértésben az alábbiakról szeretné tájékoztatni Önt:

Összefoglalás:

- Gyártóhelyi ellátási nehézségek miatt készlethiány várható a magyarországi Norditropin NordiFlex ellátásban.
- A Novo Nordisk előzetes becslése alapján az ellátás előre láthatóan 2024-ben stabilizálódik.
- A készlethiány következtében előfordulhat, hogy a betegek nem kapják meg a kezelésükhöz szükséges dózist. Ennek elkerülése érdekében szükséges, hogy a kezelőorvosok a saját klinikai megítélésükön, a releváns helyi szabályozásokon és az intézményi és/vagy szakmai protokollokon alapuló döntésük szerint, biztonságosan állítsák át őket, más alternatív – növekedési hormont tartalmazó – terápiára.
- Kérjük a kezelőorvosokat, hogy a betegek átállításának ütemezésekor vegyék figyelembe, hogy Noonan-szindróma miatti növekedés elmaradásban a Norditropin NordiFlex injekciónak nincs Magyarországon engedélyezett helyettesítő készítménye.
  Tekintettel arra, hogy a Noonan-szindrómában szenvedő betegek kezelésére más alternatíva nem áll rendelkezésre, az ő kezelésükhöz szükséges Norditropin NordiFlex mennyiség szállítását a Novo Nordisk ez év végéig biztosítja. A jelenlegi eljárásrendnek megfelelően továbbra is egyedi méltányossági engedély birtokában rendelhető társadalombiztosítási támogatással.
- Kérjük, hogy a készlethiányról és a szükséges intézkedésekről mielőbb tájékoztassák a Norditropin NordiFlex injekciót alkalmazó betegeiket, illetve gondozóikat.

A hiány enyhítésére vonatkozó intézkedések:

A kezelőorvosokat kérjük, hogy a készlethiány elkerülése érdekében a Norditropin NordiFlex Magyarországon engedélyezett terápiás alternatíváit alkalmazzák. Más típusú gyógyszeres kezelésre történő átállítás kizárólag az adott készítmények alkalmazási előírása által támasztott követelményekkel összhangban történhet, és szoros orvosi felügyeletet igényel.

A kezelőorvosoknak szóló ajánlásra vonatkozó további információk

Amennyiben rövid vagy hosszú távon nem áll rendelkezésre engedélyezett alternatív kezelés:

Mivel a növekedési hormont kapó betegek kezelése individuális, és az indikációk olyan betegcsoportot fednek le, amelybe tartozó betegek nagyon különbözőek, nem lehet egységes következtetést levonni a teljes megvonás következményeivel kapcsolatban. Mindemellett:

- Gyermekeknél, amikor a betegek elérik a várt felnőttkori testmagasságot, a szokásos klinikai gyakorlat szerint a kezelést – lefelé titrálás nélkül – rutinszerűen megszakítják anélkül, hogy emiatt bármilyen mellékhatás jelentkezne. Ezért ennél a betegcsoportnál, abban az esetben, ha a gyógyszerhiány miatt a készítményt hirtelen megvonják, specifikus közvetlen/akut következmény nem várható. A hosszú távú következményeket, mindazonáltal meghatározza az az alapbetegség vagy állapot, amiért a gyermeket kezelték.
- Felnőtteknél a növekedési hormonnal végzett kezelés előnyei, azaz hogy a mérhető fizikai eredmények láthatóvá váljanak, a hosszú távú kezeléstől függnek, emiatt közvetlen/akut következmény megjelenése nem várható egy rövidebb ideig fennálló kezelési hiány miatt. A kezelés megvonásának hosszú távú következményei a testösszetétellel, a metabolizmussal kapcsolatos és a szív egészségét érintő szövődményekhez vezethetnek, valamint kihatással vannak a beteg általános és mentális egészségére.

A Magyarországon engedélyezett lehetséges alternatívával történő helyettesítés:

Gyógyszerbiztonsági szempontból az új beadóeszköz használatára való átállás az elsődleges kockázat.

A növekedési hormonnal végzett kezelés során az alternatív készítményre történő átváltás lehetséges következményeként a rendelkezésre álló irodalom az alábbi aggályokról számol be: az új eszköz használatának megtanulása miatt jelentkező adagolási ill. kezelési hibák, valamint a beteg-család frusztrációja és szorongása miatt jelentkező csökkent adherencia.[1]

A fenti kockázatok csökkentése érdekében a betegeknek fokozott támogatásra van szükségük, amíg meg nem tanulják az új eszköz használatát.

A számba vehető kezelési lehetőségek:

A betegek kezelésének megkezdésére vagy korábbi kezelésük folytatására az alábbi táblázatban szereplő Magyarországon engedélyezett növekedési hormont tartalmazó alternatívákat lehet alkalmazni:

Terápiás javallatok gyermekeknél	**Növekedési hormont tartalmazó alternatívák**
A növekedés elmaradása a növekedési hormon hiánya (GHD-growth hormone deficiency) miatt	Genotropin® Humatrope® Nutropin® Omnitrope® Saizen®
A növekedés elmaradása leányoknál gonad dysgenesis (Turner-szindróma) miatt	Genotropin® Humatrope® Nutropin® Omnitrope® Saizen®
Növekedési retardáció krónikus vesebetegség miatt gyermekeknél pubertáskor előtt	Genotropin® Humatrope® Nutropin® Omnitrope® Saizen®
A gesztációs kornak megfelelő testhossznál kisebb (SGA – Small for Gestational Age) testhosszal született gyermekek növekedési zavara, ha a gyermekek a 4. életévükre sem hozták be növekedési lemaradásukat	Genotropin® Humatrope® Omnitrope® Saizen®
Növekedéselmaradás Noonan-szindróma miatt	
A növekedés és a testösszetétel javítása megfelelő genetikai vizsgálattal igazoltan Prader-Willi szindrómában (PWS) szenvedő gyermekeknél	Genotropin® Omnitrope®

Terápiás javallatok felnőtteknél	------
Felnőttkori kezdetű növekedésihormon hiány: Növekedési hormon-hiány önmagában vagy több hormon hiányával együtt, (hypophysis alulműködés), hypophysis-betegség, hypothalamus-betegség, műtét, koponyabesugárzás, vagy traumás agysérülés miatt.	Genotropin® Humatrope® Nutropin® Omnitrope® Saizen®
Gyermekkori kezdetű növekedésihormon-hiány: Azoknak a betegeknek, akik veleszületett, genetikai, szerzett vagy idiopathias ok miatt gyermekkorukban a növekedési hormon hiányban szenvedtek	Genotropin® Humatrope® Nutropin® Omnitrope® Saizen®

Háttérinformáció az ellátási hiányról

A Norditropin NordiFlex szomatropint tartalmaz, ami bioszintetikus úton előállított humán növekedési hormon, amit számos a növekedési hormon hiányával összefüggő betegség kezelésére alkalmaznak.

A Norditropin NordiFlex ellátási hiány gyártóhelyi ellátási nehézségek következtében alakult ki, nem gyógyszerbiztonsági vagy gyógyszerminőségi ügy következménye.

A készlethiány az alábbi termékeket érinti:
Norditropin NordiFlex® 5 mg / 1,5 ml oldatos injekció
Norditropin NordiFlex® 10 mg / 1,5 ml oldatos injekció
Norditropin NordiFlex® 15 mg / 1,5 ml oldatos injekció

Felhívás mellékhatás-jelentésre

A Norditropin NordiFlex® készítménnyel kapcsolatos nemkívánatos eseményeket, köztük a gyógyszerelési hibákat vagy a Novo Nordisk alábbi elérhetőségén jelentheti:

Novo Nordisk Hungária Kft.
Buda-part tér 2.
H-1117 Budapest
Tel: +36 1 325 9161
E-mail: safety-hu@novonordisk.com

vagy az OGYÉI alábbi elérhetőségein:

Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet
Postafiók 450 H-1372 Budapest

E-mail: adr.box@ogyei.gov.hu

mellékhatás-bejelentő felület: https://mellekhatas.ogyei.gov.hu/

A bejelentést elegendő csak az egyik helyre eljuttatni.

A Novo Nordisk A/S képviseletében eljáró Novo Nordisk Hungária Kft. elérhetősége

A gyógyszerhiánnyal kapcsolatban további információ a Novo Nordisk Hungária Kft. alábbi elérhetőségén kapható:

Novo Nordisk Hungária Kft.
Buda-part tér 2.
H-1117 Budapest
Tel: +36 1 325 9161
E-mail: info@novonordisk.hu.

Tisztelettel,

Dr. Heller József

orvosigazgató

Annexes

References:

1. Grimberg A et al Endocr Pract. 2012 May-Jun;18(3):307-316. doi: 10.4158/EP11217.OR. PMID: 21940275.

Original Article

CONSEQUENCES OF BRAND SWITCHES DURING THE COURSE OF PEDIATRIC GROWTH HORMONE TREATMENT

Adda Grimberg, MD[1,3,4]; Chris Feudtner, MD, PhD, MPH[2,3,4]; Catherine M. Gordon, MD, MSc[5,6,7]

ABSTRACT

Objective: To explore the effects of insurance-mandated brand switches during the course of pediatric recombinant human growth hormone (rhGH) treatment on clinical practice.

Methods: We e-mailed a 9-question, anonymous, Internet-based survey to active members of the Pediatric Endocrine Society. The survey consisted of multiple-choice and yes/no answers. Free-text comments were solicited for further explanation of responses. Quantitative answers were tabulated. Each investigator independently coded the free-text responses; themes based on codes identified by all 3 investigators in a minimum of 5 different respondents' comments were compiled and organized.

Results: Of the 812 active members of the Pediatric Endocrine Society who were e-mailed the survey, 231 responded. Two hundred eight respondents reported switching a patient's regimen from one rhGH product to another, and of these, 50% experienced repeated switches. Switches occurred for each commercially available rhGH brand. Frequent concerns noted by respondents involved dosing errors and treatment lapses from having to learn a new device and impaired adherence related to patient-family frustration and anxiety. Anti-GH antibodies, measured by only 3 endocrinologists when switching a patient's regimen from one brand to another, were negative before and after the product switch. When a patient switched rhGH brands, the most frequently reported time involvement for endocrine office staff was 2 hours for paperwork, 1 hour for device instruction, and 1 hour for "other" (mostly related to telephone reassurance).

Conclusion: GH brand switches may adversely affect patient care and burden pediatric endocrinology practices. **(Endocr Pract. 2012;18:307-316)**

Abbreviations:
FDA = Food and Drug Administration; **hGH** = human growth hormone; **rhGH** = recombinant human growth hormone

INTRODUCTION

Human growth hormone (hGH) treatment began with the National Hormone and Pituitary Program, which from 1963 to 1985 provided nearly 8000 US children with hGH extracted from cadaveric pituitary glands until the program was terminated abruptly due to the transmission of Creutzfeldt-Jakob disease (1). Development of recombinant DNA technology enabled expression of hGH in *Escherichia coli* (2) and subsequently purification of the peptide product (3). The first recombinant peptide was methionyl-hGH, the extra N-terminal methionine inserted by the bacterial process of protein synthesis. Methionyl-hGH was found to have bioactivity comparable to that of pituitary hGH (3) and to a later recombinant product with amino acid identity to endogenous hGH (4). The advent of recombinant hGH (rhGH) peptides led to mass production by multiple manufacturers who then developed injection

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From the [1]Diagnostic and Research Growth Center, Division of Pediatric Endocrinology and Diabetes, [2]Department of Medical Ethics and PolicyLab, [3]Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [4]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [5]Bone Health Program, [6]Divisions of Adolescent Medicine and Endocrinology, Children's Hospital Boston, Boston, Massachusetts; [7]Harvard Medical School, Boston, Massachusetts.
Address correspondence to Dr. Adda Grimberg, Scientific Director, Diagnostic and Research Growth Center, Division of Pediatric Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Suite 11NW30, 34th Street and Civic Center Blvd, Philadelphia, PA 19104. E-mail: grimberg@email.chop.edu.
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devices for their products (5). As the market expanded and patents expired, "generic" versions of rhGH (referred to as follow-on or biosimilar rhGH) also appeared (6-9).

Insurance providers originally covered pediatric rhGH treatment if the manufacturer of a particular rhGH product had obtained US Food and Drug Administration (FDA) approval for the specific therapeutic indication of a given patient. As multiple manufacturers obtained FDA approval for the various indications, and appreciation grew for the sequence identity and hence indistinguishable bioactivity of the various rhGH peptides, the different products started to be viewed as equivalent (4,8,10). Thus, insurance providers have been increasingly adopting formulary preference coverage strategies. Because the preferred brand may change when a patient changes their insurance provider, or when an insurance provider renegotiates their contracts with the various rhGH manufacturers, the formulary preference strategy may mandate brand switches during the long-term course of rhGH treatment in children and adolescents.

In this study, we sought to explore pediatric endocrinologists' assessments of the consequences of rhGH brand switches on clinical practice.

METHODS

A brief, anonymous survey was created in SurveyMonkey (SurveyMonkey, Portland, Oregon), consisting of 9 questions with multiple-choice and yes/no responses (Box 1). Free-text comments were solicited for further explanation of responses. The survey, titled "LWPES: Drugs and Therapeutics Committee Survey," was emailed to active members of the Pediatric Endocrine Society (PES, formerly named in honor of Lawson Wilkins) and left open for 30 days during the summer of 2009. One reminder e-mail was sent to the membership to encourage participation.

Responses to the survey were collated and analyzed by standard descriptive statistics using Excel (Microsoft Corp, Redmond, Washington). Following established qualitative data analysis–grounded theory methods (11), the investigators first performed a preliminary review of the respondents' free-text comments, and developed a set of standardized code words or phrases (such as "lapse in treatment," "safety concerns," or "more time on reassurance, retraining"), with clear definitions of what each code word or phrase meant, with each code word or phrase describing a potential characteristic of the free-text comments. Each investigator then independently reviewed all of the free-text comments and labeled each comment with applicable code words or phrases. Only those free-text comments labeled by all 3 investigators with a particular code were regarded as exhibiting that code's characteristic. The investigators then worked with only those codes (from the entire initial set of codes) that were exhibited in a minimum of 5 different survey respondents' comments, aggregating these common codes into broader themes (such as "drug and device focused" or "autonomy focused") and organizing these themes in terms of the consequences implied by the respondents' comments.

RESULTS

The survey was e-mailed to the 812 active members of the Pediatric Endocrine Society. Pediatric Endocrine Society membership consisted of 747 physicians from the United States, 32 from Canada, and 1 to 7 from each of another 18 countries. Two hundred thirty-one pediatric endocrinologists (28%) responded to the survey. Two hundred eight respondents (90%) reported switching the regimen of a pediatric patient from one rhGH product to another, and of these, 50% reported repeated switches. Switches occurred to each of the commercially available rhGH brands. Three survey questions explored potential adverse effects of rhGH brand switches on clinical practice (Table 1). Free-text comments with unanimous, independent coding by the 3 investigators were organized into a thematic diagram of concerns and consequences stemming from the mandated brand switches (Fig. 1).

Consequences for Patients and Families

The survey queried respondents regarding potential diminished effectiveness (eg, growth deceleration) due to brand switching. Although a few respondents unqualifyingly reported reduced growth velocity with the new brand (and 1 respondent further noted improvement upon resumption of the original brand), most comments regarding effectiveness related the decline to decreased adherence from lapses in treatment, confusion, and errors associated with a new device. A few respondents cited adverse effects, such as pain or edema that necessitated a return to the original product, and 1 respondent reported discomfort with being mandated by the insurance provider to prescribe a follow-on rhGH product. One possible biologic explanation for diminished effectiveness from brand switches involves rhGH immunogenicity. Only 3 respondents routinely measured anti-GH antibodies when switching a patient's regimen from one rhGH brand to another, and all 3 found negative titers both before and after the switch.

Comments responding to a query on patient safety are summarized in Table 2. The most frequently reported safety concerns consisted of dosing errors and patient confusion related to different rhGH concentrations among the products, different storage requirements, and different injection devices with different reconstitution procedures and different dosing increments. Dosing errors occurred despite patient education about the new product, and the education and paperwork process itself were blamed for wasted staff time and treatment lapses.

A query regarding patient-family issues associated with switching rhGH brands elicited the most comments.

Ten respondents cited increased burning, pain, or stinging with a particular brand that adversely affected patient adherence. Many respondents offered that patients may realize they have a preference for a particular injection device (injectable vs noninjectable system, needle and syringe vs pen device, reconstitution procedures, needle size, dosing increments, and differences in pen mechanics). Most respondents reported negative patient-family reactions when brand or device preferences were ignored by insurance-mandated product switches, using words such as anxiety, annoying, distress, frustration, and unhappiness. They also reported patient-family fears and anxiety both in the quality of the insurance-mandated product relative to their current, trusted brand and in the potential for interruptions in drug delivery and disruptions in administration related to the logistics of obtaining and learning

Box 1
Brief, Anonymous Survey Entitled, "LWPES: Drugs and Therapeutics Committee Survey," E-mailed to the 812 Active Members of the Pediatric Endocrine Society

1. Have you ever switched a pediatric patient from one GH product to another?
   - Yes
   - No
2. If yes, please click on the brands you have switched to (you may choose more than one).
   - Genotropin
   - Humatrope
   - Norditropin
   - Nutropin
   - Saizen
   - Tev-Tropin
   - Can't recall
3. Have there been repeated switches?
   - Yes
   - No
4. Have you experienced any effect of switching on efficacy (eg, growth deceleration)?
   - Yes
   - No
   - If yes, please explain:
5. Have there been any safety concerns associated with the switching?
   - Yes
   - No
   - If yes, please explain:
6. Have there been any patient-family issues associated with the switching?
   - Yes
   - No
   - If yes, please explain:
7. Have you routinely measured anti-GH antibodies when switching from one product to another?
   - Yes
   - No
8. What were the findings of such measurements?
   - Titers negative before and after the switch
   - Titers positive before and after the switch without significant change in levels
   - Titers converted from negative to positive with the switch
   - Titers positive and rose substantially higher after the switch
9. How much time do you estimate is spent by you and your office staff when a child is switched from one hGH brand to another? In hours:
   a. For paperwork?
   b. For device instruction?
   c. For other?
   d. Additional comments:

about a new product. Learning to use a new product led to patient-family frustration and anxiety, inconvenience, wasted time, confusion, and dosing errors. Two respondents reported loss of child independence in self-administering rhGH because of difficulties with the new product, and many respondents related the negative patient-family reactions to effects on regimen adherence. Lapses in treatment were also a common concern, related to the paperwork, delivery, and training required to initiate treatment with a new product.

Consequences for Professionals and Science

rhGH brand switches also had repercussions for the prescribing endocrinology practices. Figure 2 shows the estimated time spent by pediatric endocrinologists and their office staff when a patient's regimen was switched from one rhGH brand to another. Three endocrinologists reported spending less than 1 hour for the paperwork, 1 reported less than 1 hour for reassurance, and 2 reported less than 1 hour for instruction, especially when the patient was already comfortable with injections. Conversely, 1 respondent reported more than 10 hours for the paperwork. Two had difficulty quantifying an average duration.

Sixty-three respondents offered written comments expanding on time commitment. The "other" activities were most commonly identified as telephone conversations with patient-families explaining why the switch was occurring, reassuring them and allaying their anxieties about the new product and the process, and following up afterwards to ensure there were no treatment lapses. "Other" also included ancillary activities like insurance appeals and notifying GH case managers, home care delivery companies, and pharmacies about the impending switch. Many children and adolescents receiving rhGH treatment are followed in postmarketing surveillance studies. Because these GH registries are brand-specific, termination paperwork for the current registry and enrollment into the registry associated with the new rhGH brand was cited as another time-consuming activity related to brand switches. Further, such switches lead to loss of long-term follow-up data in the registries because there is no way to track patients from one registry to another.

Many of the respondents voiced frustration and scorn at the role insurance providers have in this process. While some rhGH brand switches occur because of clinical responses to the first product, most are mandated by insurance formulary preference coverage; the preferred formulary brand(s) may switch either when a patient-family changes their insurance provider or when the extant insurance provider alters its contractual arrangements with the rhGH manufacturers, which are renegotiated every 1 or 2 years. Such rhGH brand switches are mandated for the primary purpose of minimizing insurance provider costs, while the time required of the prescribing endocrinologists and their staff is not reimbursed. This frustration was further compounded by the lack of assistance from insurance providers in streamlining the process. Several respondents complained that the rhGH brand switch paperwork and authorization process was "like starting from scratch" for a given patient, that each insurance company's paperwork and policies were different, that insurance providers did not notify the practitioners in a timely fashion, and that approval for the new rhGH product often took weeks. Some added that insurance providers may deny rhGH for patients who had previously been covered, leading to a lengthy appeals process, and lack of communication between the insurance provider and their contracted pharmacy further increases the paperwork burden. While several respondents reported that the time involved in the rhGH brand switch process was disruptive to their practice, 6 reported mitigating the impact by outsourcing the patient-family device retraining to nurses employed by the rhGH manufacturer.

DISCUSSION

rhGH brand switches during the course of treating a pediatric patient have become commonplace and involve all the commercially available products. Switches in rhGH preparations can result in negative effects on overall treatment effectiveness as evidenced by lapses in treatment,

Table 1
Numbers of Responses and Comments to the Survey Questions Exploring Potential Effects of Recombinant Human Growth Hormone Brand Switches on Clinical Practice

Question	No. of respondents	No. of *yes* responses	No. of *no* responses	No. of comments
Any effects on efficacy (eg, growth deceleration)?	182	15	167	23
Any safety concerns?	185	24	161	25
Any patient-family issues?	186	123	63	121

reduced adherence, and dosing errors. Safety concerns can also heighten anxiety among affected families, which can increase the uncompensated workload for a pediatric endocrine practice.

Insurance-mandated formulary brand preferences are not unique to rhGH. Concerns have been raised about differences in potency and bioavailability between brand and generic preparations of drugs with narrow therapeutic ranges, such as anticonvulsant drugs (12-15) and levothyroxine (16-18). For example, 2 recent case-control studies found an increased risk of emergency department or hospital-level care for epilepsy-related events associated with switches to A-rated generic anticonvulsant formulations (19,20). Unlike other medications for which pharmacies automatically switch brands upon filling a prescription, rhGH brand switches require resubmission of paperwork for a new preauthorization review. This time-consuming and unreimbursed process for the prescribing endocrinologist and office staff is stressful to the clinician and patient-family not only because previously covered rhGH treatment may be denied, but also because rhGH brand switches require reeducation of patients and families in administering rhGH with their new product's injection device, resulting at best in only inconvenience and at worst in potential dosing errors. Denial of previously covered rhGH therapy for a patient midtreatment is particularly frustrating because it makes rhGH coverage seem fickle and blind; the patient's previous therapeutic responsiveness is both ignored by the denial of ongoing treatment and compromised by the resultant lapse in treatment until the denial can be appealed, which is not always successful.

Another consequence of brand switching is the loss of longitudinal data in the rhGH registries. Because the rhGH registries are proprietary to the various rhGH manufacturers who fund them, when patients switch brands, they no longer qualify for their current registry and must be enrolled

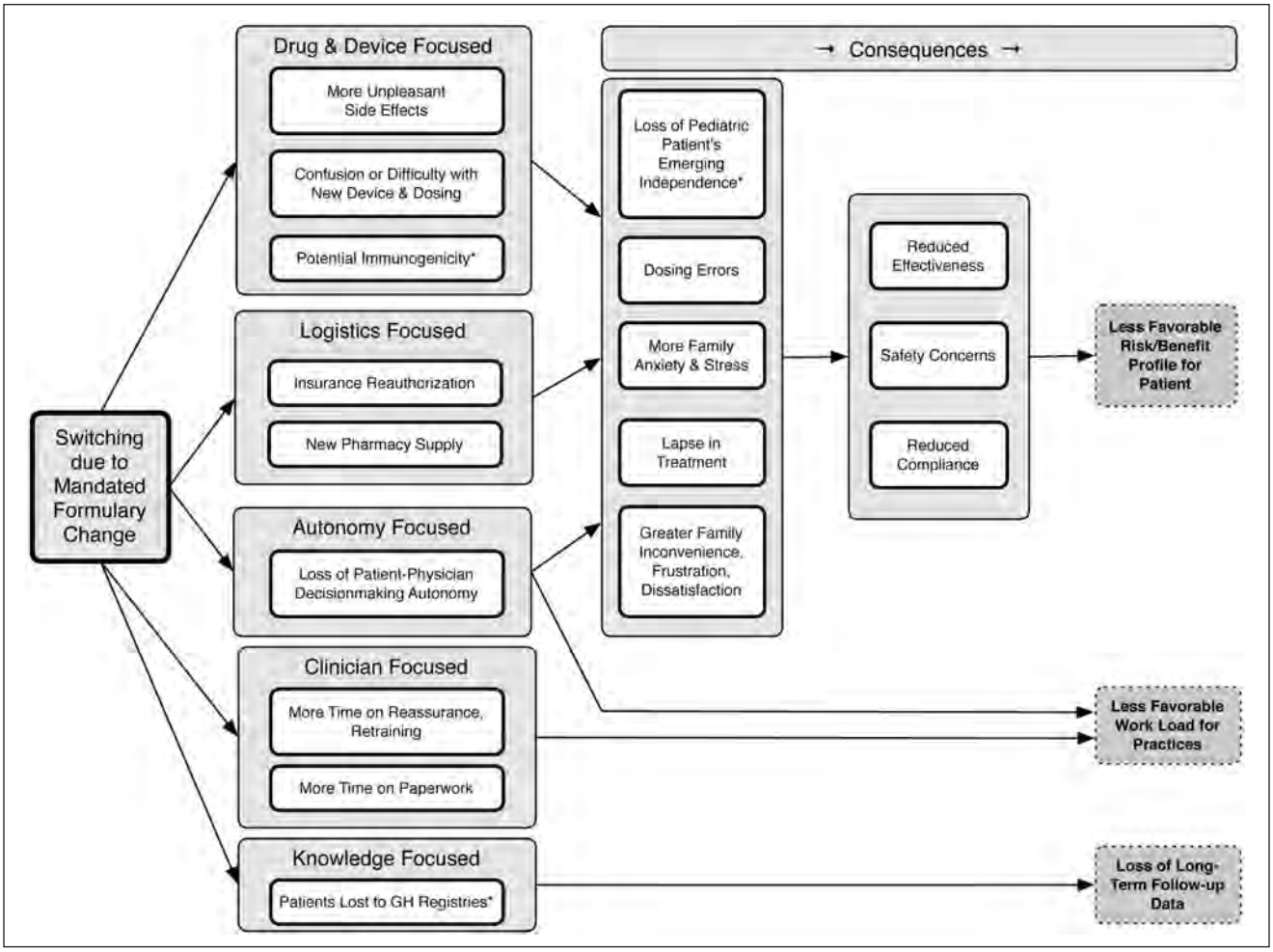

Fig. 1. Thematic diagram of observations and consequences stemming from mandated recombinant human growth hormone brand switches. Themes were scored from the free-text comments provided across all survey questions and were included if they were supported by comments, each with unanimous investigator consensus, from a minimum of 5 different survey respondents. Those marked with an asterisk had fewer than 5 supporting comments, but were thought by the investigators to raise important issues worthy of consideration.

de novo in the registry of the new brand. There is currently no way of tracking patients across registries. The more frequently switches occur, the more disjointed the available follow-up data will become. The major strength of these postmarketing surveillance studies, originally mandated by the FDA upon commercial introduction of rhGH in 1985, has been the longitudinal nature of their data. More than 520 000 patient-years experience with rhGH have been recorded up to January 2010 (personal communication, Pfizer, New York, New York; Genentech Medical Affairs, South San Francisco, California; Charmian Quigley, MBBS, Eli Lilly and Company, Indianapolis, Indiana; John Germak, MD, NovoNordisk Inc, Princeton, New Jersey; and Viatcheslav Rakov, MD, NovoNordisk Health Care AG, Zurich, Switzerland) and have contributed significantly to our understanding of rhGH effectiveness and safety. Frequent brand switching necessitates the creation of a single rhGH registry to monitor patients across all rhGH brands and to continue collecting such longitudinal data.

Although brand switching may raise the theoretical concern of increased immunogenicity, this assumption was not supported by our limited data. Only 3 endocrinologists reported routinely measuring anti-GH antibodies when switching a patient's regimen from one rhGH brand to another, and all 3 found negative titers both before and after the switch. This may reflect secular trends associated with the evolution of the hGH products. Immunogenicity was found among patients receiving pituitary hGH and depended on the product preparation and purification (21-23). Methionyl-hGH, with its novel N-terminus, was even more immunogenic, although growth attenuation from high affinity anti-GH antibodies was uncommon (23-25). Human sequence rhGH had low immunogenicity and, again, rare immune-mediated growth attenuation (26-28). The exception remains patients with GH gene deletion, who had never expressed endogenous GH and thus expectedly produced growth-attenuating anti-GH antibodies on exposure to exogenous hormone (29). Because current products all possess native sequence, their main immunogenic potential derives from process-related and product-related impurities, which are present in very low concentrations and in different composition among the different products. Switching brands would increase a patient's exposure to such impurities and hence, potentially increase the incidence of immune reactions. The finding that so few of the survey respondents routinely measure anti-GH antibodies probably reflects the confidence of the pediatric endocrine community in current rhGH production and purification processes, now 1 and even 2 decades after the reports of rare immunogenicity from earlier rhGH products (30).

The principal limitation of this study is that the 28% response rate may have introduced nonresponse bias. Of note, not all members of the Pediatric Endocrine Society clinically prescribe rhGH; some limit their practice to patients with diabetes mellitus, and others are investigators who do not participate in patient care. Without practice data, we could not define more sharply our denominator.

Table 2
Responses to the Question Regarding Safety Concerns From Recombinant Human Growth Hormone Brand Switches

Comment	Respondents, No.
Dosing errors and patient confusion	14
Potential for immunogenicity effects	4
Injection site pain or burning with the new product	4
New-onset rashes related to the new product (of these, 1 required emergency department evaluation)	2
Concerns related to the sparse safety data available for follow-on recombinant human growth hormone products	2
Mandated switch of a neonate from a preservative-free to a preservative-containing product	1
Presumed local allergic reaction (stopped with change to a third product)	1
Optic nerve swelling (developed in a patient with Turner syndrome after an insurance-mandated brand switch that led to a 6-month discontinuation of recombinant human growth hormone treatment and then resumption of the original brand)	1
Severely deficient patients being without product for 1 or 2 months	1

We e-mailed the entire Pediatric Endocrine Society active membership because pediatric endocrinologists are the principal prescribers of rhGH for pediatric patients. Although this approach limited the sampling frame, it focused on the most pertinent population and allowed endorsement of the brief questionnaire by a legitimizing professional association, methods shown to improve physician survey response rates (31). Our response rate, while low, was comparable to that obtained by an e-mail survey of the Georgia Chapter of the American Academy of Pediatrics after 2 mailings (26%) (32) and the e-mailed 2007 National Physician Survey (30%) despite various unsuccessful attempts to increase rates from the 2004 survey (33).

Our study design precludes inference of prevalence frequencies. Although nonresponse bias seems less operant in surveys of physicians than in the general population (34,35), it remains a possibility (36). Even in the extreme scenario wherein all the Pediatric Endocrine Society members who did not respond to the survey had no concerns whatsoever, a minimum of 2% of the Pediatric Endocrine Society membership reported diminished effectiveness, 4% had safety concerns, and 18% cited adverse patient-family consequences. As investigators of the first study exploring adverse unintended consequences of rhGH formularies, we sought to determine the potential existence and types of such consequences, and, on the basis of the results, determine whether more robustly designed studies are warranted on the subject.

Although we cannot comment on prevalence or magnitude, findings from our exploratory survey indicate that rhGH formularies can lead to adverse unintended consequences. The high cost of rhGH therapy and its expanding market create strong pressure for use of cost-containing methods like insurance-mandated formulary brand preferences. Since the FDA approved rhGH treatment for idiopathic short stature in 2003, about 1% of all US children became eligible for treatment with rhGH, with a potential cost of approximately US $40 billion (37). Thus, insurance-mandated formulary brand preferences are likely to increase in practice. This study has identified problematic consequences of brand switching, a requisite part of formulary preference strategies, and thereby suggestions for improvement by the insurance providers and rhGH manufacturers, who determine the preferred brands (Table 3). By streamlining the process and providing timely notification, insurance providers can prevent lapses in treatment and reduce clinician burden, patient-family anxiety, errors, and overall cost to the health care system. Should the current cumbersome system continue, careful consideration should be given to reimbursing pediatric endocrine practices for the time and effort imposed by the brand-switching process. Monitoring the effects of rhGH brand switching

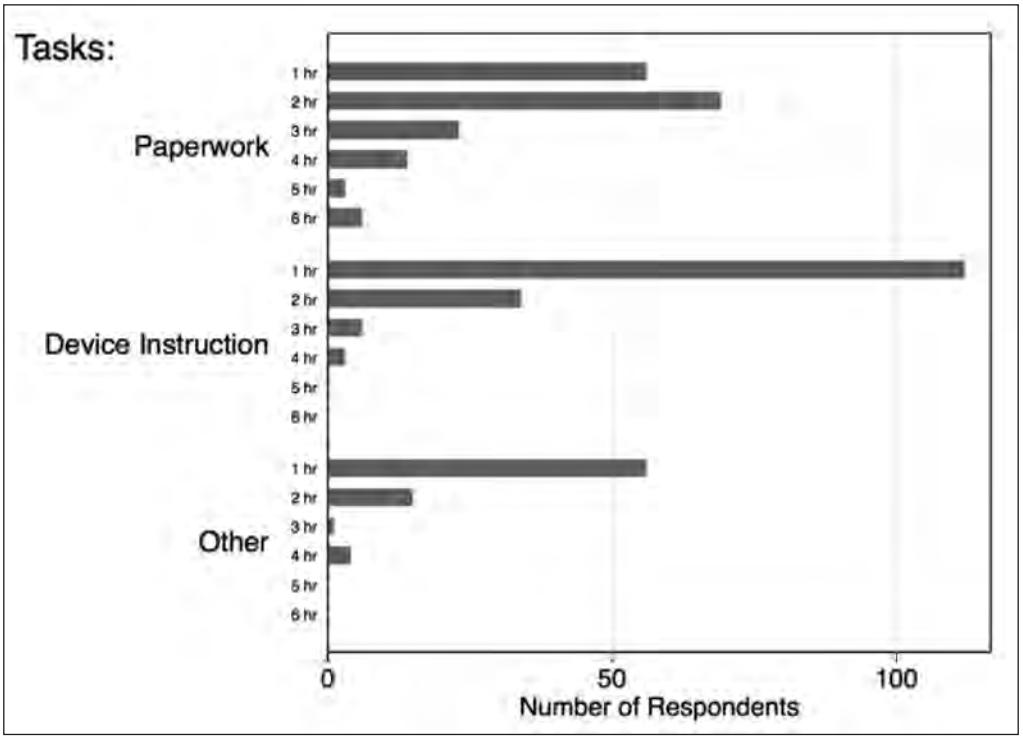

Fig. 2. Time spent by pediatric endocrinologists and their staff when a patient's regimen is switched from one recombinant human growth hormone brand to another.

Table 3
Identified Problems From Recombinant Human Growth Hormone Brand Switches and Their Potential Solutions

Problem	Solution by recombinant human growth hormone manufacturers	Solution by insurance providers
Dosing errors	Troubleshoot for the potential for dosing errors when designing injection devices: • Nonconfusing dosing increments • Obvious dosing with easy readability and no or minimal mathematical conversions • Automatic blocking or correcting mechanisms for misdialing • Strategies to prevent pen-cartridge mismatching	…
	Provide patient-family with quality instruction in using the new injection device and routine telephone follow-up afterwards to ensure proper use	
Treatment lapses	Telephone follow-up with patient-families to ensure they did not experience a lapse in treatment or other difficulties	Timely notification to patient-families and prescribing physicians
		Streamline the process for prescribing clinicians (see below)
Patient-family anxiety about the switch	…	Provide timely, easy-to-comprehend explanatory materials in anticipation of the switch process that summarize: • The reason for the mandated brand switch • Patient-family options regarding the formulary brand choice(s) • How the new preferred brands compare with the current formulary brands (complete with pictures) • Step-by-step algorithm guiding families through the process replete with contact information for directing questions and any appeals processes
Burden to prescribing clinicians	…	Streamline the process by: • Standardizing the forms • Using forms prepopulated with patient information already in the insurance system from their currently approved recombinant human growth hormone use • Making it a 1-step prescribing process: the clinician completes and submits 1 form to the insurance company, which then reviews it and directs it to their contracted pharmacy/delivering agent, which then activates and delivers the recombinant human growth hormone to the patient (rather than the clinician getting approval de novo from the insurance company first and then separately determining which pharmacy/delivering agent they must use and making arrangements to actually get the recombinant human growth hormone to the patient)

should continue, with special attention to effects on adherence, even treatment cessation, and health outcomes.

CONCLUSION

Insurance-mandated brand switches during the course of pediatric rhGH treatment are justified as a cost-containing strategy for an expensive medication with 7 different brands offering the identical active hGH molecule. However, the various brands differ in their diluents, injection devices, and services offered to patients and professionals. Effects of rhGH brand switches observed by pediatric endocrinologists can be categorized as relating to the drug or device, logistics, autonomy, and clinician and scientific knowledge. These effects lead to decreased effectiveness; safety concerns; reduced compliance; and, ultimately, less favorable risk-to-benefit profile for the patient, less favorable workload for the endocrine practices, and loss of long-term follow-up data for the GH registries. While this study is based on pediatric rhGH treatment, its findings may illustrate more general issues of payment encroaching on what had been an autonomous decision-making process between physicians and patients.

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DISCLOSURE

In the past 3 years, the Endocrine Divisions of the Children's Hospital of Philadelphia and Children's Hospital Boston have been participating in the GH registries of all the major GH manufacturers (Eli Lilly, Genentech, NovoNordisk, Pfizer, and Serono). Dr. Adda Grimberg received an investigator-initiated research grant from Genentech and honoraria and reimbursed travel expenses for presenting her research at GH meetings sponsored by Pfizer and NovoNordisk (although Dr. Grimberg has never served on any speakers' bureaus). Dr. Catherine M. Gordon received partial salary support to codirect the Clinical Investigator Training Program, fellowship program sponsored by Harvard/MIT and Pfizer/Merck. No form of payment was given to anyone to produce the manuscript. Dr. Chris Feudtner has no multiplicity of interest to disclose.

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