Long-Term Safety of Recombinant Human Growth Hormone in Turner Syndrome

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Context: Turner syndrome (TS) affects more than 50,000 girls and women in the United States. The National Cooperative Growth Study (NCGS) has collected efficacy and safety data for 5220 TS children treated with recombinant human GH (rhGH) during the last 20 yr.

Objectives: Our objective was to determine frequencies of specific targeted adverse events (AEs) and additional AEs of interest in TS patients. Corresponding safety data in non-TS patients or normal populations were compared for selected AEs.

Methods: Patients may be enrolled at rhGH initiation and followed until discontinuation. Investigators submit AE reports describing any event that is potentially rhGH related or is a targeted event.

Results: The Genentech Drug Safety department received 442 AE reports for TS NCGS patients as of June 30, 2006, including 117 serious AEs. Seven deaths occurred; five resulted from aortic dissections/ruptures. The incidence of certain events known to be associated with rhGH (targeted events), including intracranial hypertension, slipped capital femoral epiphysis, scoliosis, and pancreatitis, was increased compared with other non-TS patients in NCGS. There were 10 new-onset malignancies that occurred, including six in patients without known risk factors. Type 1 diabetes also appeared to be increased compared with other NCGS groups.

Conclusions: Children with TS who were treated with rhGH exhibit an increased underlying risk for selected AEs associated with rhGH and for type 1 diabetes, which is likely unrelated to rhGH. The aortic dissection/rupture incidence reflects the higher baseline risk for these events in TS, was consistent with current epidemiological data in smaller TS populations, and is likely unrelated to rhGH. It is not known whether the reported malignancies represent an inherently increased risk in TS patients. Twenty years of experience in 5220 patients indicates no new rhGH-related safety signals in the TS population. The NCGS and similar registries, although focused on the years during rhGH treatment, may also be a window into the natural history of TS in childhood. **(*J Clin Endocrinol Metab* 93: 344–351, 2008)**

Turner syndrome (TS), characterized by an abnormal or missing X chromosome, occurs in approximately one in 2500 live female births (1). In the United States, at any one time, it is estimated that more than 50,000 girls and women are affected with this disorder. Individuals with TS may have or will develop a variety of health problems, including cardiac and vascular malformations, such as aortic coarctation, bicuspid aortic valve, and aortic dilation, dissection, and rupture (2). Other physical and medical issues include short stature, gonadal dysgenesis, hearing loss, renal malformations, hypothyroidism, glucose intolerance, and the consequences of fetal lymphedema such as webbing of the neck with low posterior hairline (3). The most common causes of death in young TS patients are congenital cardiac malformations and aortic dissection/rupture, both described before

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Abbreviations: AE, Adverse event; CI, confidence interval; CRI, chronic renal insufficiency; DM, diabetes mellitus; GHD, GH deficiency; IH, intracranial hypertension; NCGS, National Cooperative Growth Study; OGHD, organic GHD; rhGH, recombinant human GH; SAE, serious adverse event; SCFE, slipped capital femoral epiphysis; SIR, standard incidence ratio; TS, Turner syndrome.

the introduction of GH therapy (4). Short stature is the most common physical feature of TS. Although organic GH deficiency (OGHD) is not a feature of TS, the efficacy of recombinant human GH (rhGH) in increasing linear growth and final height in TS patients is well documented (5–7).

The National Cooperative Growth Study (NCGS) is an open-label, multicenter, postmarketing surveillance study established by Genentech, Inc., in 1985 to monitor the safety of rhGH (Protropin, and later Nutropin, Nutropin AQ, and Nutropin Depot) in the treatment of pediatric patients with growth disorders, including idiopathic GH deficiency (GHD), OGHD, idiopathic short stature, and chronic renal insufficiency (CRI), as well as TS. The NCGS represents the largest database of TS individuals in the United States. Although reports on TS have been generated previously from this study (8, 9), the current report is the first detailed safety examination of all 5220 TS patients in the registry. These data enable a careful evaluation of the safety of rhGH in these patients and afford a better understanding of the natural history of medical disorders associated with this condition.

Patients and Methods

Patients may enter the study when a Genentech rhGH therapy is initiated, even if previously treated with another GH, and can be followed until rhGH therapy is discontinued or they transfer to another company's GH product. Investigators are required to submit an adverse event (AE) or serious AE (SAE) report to the Genentech Drug Safety Department describing any event that may potentially be related to rhGH. SAEs are defined as events that are fatal, life threatening, require hospitalization, result in disability, necessitate surgical intervention, and/or result in a congenital anomaly or birth defect. Investigators are also instructed to report all protocol targeted events, regardless of the perceived relationship to rhGH, including malignancy (new onset or recurrence), diabetes mellitus (DM), slipped capital femoral epiphysis (SCFE), intracranial hypertension (IH), scoliosis, and pancreatitis, as specifically described in the study protocol. Parameters to determine the presence of these diagnoses are determined by the investigator. Although patients are no longer followed in the NCGS once rhGH is discontinued, all subsequently reported events are recorded.

Nontargeted events, particularly if they are common or expected (*e.g.* thyroid disorders, ear infections, lymphedema, or hypertension), are likely not reported consistently and, therefore, underestimated. However, targeted events are less likely to be underestimated systematically because investigators are required to report all cases as SAEs or AEs. For categories in which relevant data were available, standard incidence ratios (SIRs) and 95% confidence interval (CI) were calculated. The SIR is defined as the number of observed cases (reports) divided by the number of expected cases based on the age-adjusted incidence rates in the general population as applied to the years of rhGH exposure among TS patients.

Results

As of January 1, 2006, 54,996 patients (35% female), representing 192,345 patient years of treatment with Genentech rhGH products, were enrolled in the NCGS. As of June 30, 2006, 5,220 (9.5% of the total NCGS) were patients diagnosed with TS and account for 21,151 (11.0% of the total NCGS) patient years of GH therapy. Age at enrollment was 0.1–21.2 yr for TS patients, with a mean age of 9.8 yr. Of TS enrollees, 85% were 3–15 yr in age.

Safety data are presented in four categories: 1) overall safety, including deaths; 2) protocol targeted events associated with or exacerbated by rhGH (IH, SCFE, scoliosis, pancreatitis, DM); 3) events known to occur with increased frequency in TS patients (cardiac/aortic events, hypertension, lymphedema, thyroid disorders, ear disorders); and 4) other serious events [*e.g.* malignancies (a targeted event), other SAEs reported in more than two patients].

These categories may overlap because many conditions observed in patients receiving rhGH (*e.g.* scoliosis, DM) occur with a higher frequency in untreated TS patients. We report these occurrences as events associated with rhGH. In some cases, safety data for non-TS patients enrolled in the NCGS are provided for comparison.

Overall safety findings

Overall, 4084 AEs have been reported in the NCGS population. Among the 5220 TS patients enrolled, 442 primary AE reports were received by the Genentech Drug Safety Department, compared with 3642 AEs in the non-TS population. These 442 AEs account for 10.8% of all NCGS AE reports. Of the 442 AEs reported in TS patients, 117 were considered SAEs, accounting for 7.5% of all NCGS SAE reports. The incidence of AEs as a percentage of enrolled TS patients was 8.5% (7.3% for the rest of the NCGS); the incidence of SAEs for TS patients was 2.2% (2.9% for the rest of the NCGS). The incidence was based on the number of AE or SAE reports rather than the number of patients; the actual incidence may be lower because some patients may have experienced more than one AE or SAE. The cutoff date for non-TS NCGS AE data was January 1, 2006 and for TS AE data was June 30, 2006. Overall NCGS enrollment increased by 2.8% in 2006 between January 1st and June 30th.

A total of 174 deaths had been reported to the NCGS registry. Seven deaths (4% of NCGS death reports) were reported in TS patients compared with 167 deaths reported in the non-TS population. Five of the seven deaths were caused by aortic dissection or rupture (see *Cardiac/aortic events* and Table 1), one was related to the development of an angiosarcoma (see *Malignancies*

TABLE 1. Fatal aortic events reported in NCGS-enrolled patients with TS

Patient age (yr)	Cardiac event	rhGH exposure	Medical history
14	Fatal ruptured aortic aneurysm	2 yr; off 3 months	Surgical repair aortic coarctation at age 8 yr
16	Fatal ruptured aortic aneurysm	4 yr	GI bleed before rhGH start
16	Fatal ruptured aortic dissection	9 yr	Dilation procedure for coarctation; died postop
15	Fatal ruptured aortic aneurysm	6 yr	Bicuspid aortic valve
15	Fatal ruptured aortic aneurysm	7 months; off 21 months	Chest x-ray, EKG, and ECHO normal

ECHO, Echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; postop, postoperatively.

and Table 2), and the remaining death was due to aspiration, occurring approximately 2 yr after starting rhGH therapy in a 5 yr old with cerebral palsy and congenital heart disease. The most common cause of death in the NCGS registry overall was central nervous system tumor (new onset or recurrence), which is a frequent preexisting condition resulting in OGHD. The incidence of death among TS patients was 0.1%, compared with 0.3% for non-TS enrollees.

Targeted AEs associated with or exacerbated by rhGH

IH

There were 12 cases of IH that have been reported in TS patients; this represents an incidence of 0.23% in the TS population, compared with 0.11% in non-TS patients in the NCGS. The IH frequency in TS patients was approximately 8-fold greater than that occurring in patients with idiopathic short stature, 2-fold greater than that in patients with idiopathic GHD, similar to the incidence reported in patients with OGHD, and 50% lower than in patients with CRI. The large majority of patients restarted rhGH after their event of IH (usually at an initially reduced dose).

SCFE

The incidence of SCFE in the TS population was 0.24%, compared with 0.15% for the non-TS patient population. Among the 13 reports of SCFE in TS patients, 11 were characterized by unilateral involvement, or the degree of involvement was not specified, and two were described as bilateral involvement. Most patients with SCFE underwent surgery. Five additional patients with TS (0.1%) were reported to have SCFE at NCGS entry, compared with 26 (0.05%) non-TS patients enrolled in the rest of the NCGS. No recurrent SCFE occurred in these five patients.

Scoliosis

The incidence of scoliosis in TS patients was 0.69%, compared with 0.39% among non-TS patients. Of the 36 reports of scoliosis in TS patients, 16 were considered to be a progression of preexisting scoliosis. In the remaining 20 cases, scoliosis was described as new in onset, or a prior history was not specified. Most events (25 of 36) of scoliosis were considered to be nonserious.

Pancreatitis

Three reports of pancreatitis in patients with TS were submitted. Two patients were reported to be hospitalized; one of these patients had a history of type 1 DM and experienced ketoacidosis in association with the episode of acute pancreatitis. There were only six reports of pancreatitis in the rest of the NCGS, indicating a disproportionate number in TS.

DM

The incidence of DM in TS patients was 0.19%, compared with 0.10% for the non-TS population. Of the 10 TS patients affected, eight represented type 1 DM, and two represented type 2 DM. Additional reports of glucose intolerance or hyperglycemia were received but are not discussed in this analysis. A comparison of the incidence of type 1 DM in TS patients with that of the age-matched general population indicates a SIR (observed cases/expected cases) of eight of 3.8 or 2.1 (95% CI 0.92, 4.18). A SIR analysis was not performed for type 2 DM due to the lack of accurate background rates in the general pediatric population and the small number of reports in TS patients.

AEs occurring with increased frequency in TS patients

Cardiac/aortic events

There were 17 serious cardiac events that have been reported in TS patients, including five fatal aortic dissections/ruptures (Table 1), five nonfatal coarctations, three pericardial effusions, one congestive heart failure (history of cardiomyopathy), one right heart failure (history of sleep apnea), one left ventricular hypertrophy (prior aortic stenosis), and one valve abnormality. No aortic dissections or ruptures were reported in any non-TS patient in the NCGS.

Hypertension/lymphedema, thyroid disorders, ear disorders

Several conditions commonly associated with TS were reported, including hypertension (n = 4), lymphedema (n = 4), Graves' disease (n = 4), hyperthyroidism of unspecified type (n = 1), hypothyroidism (n = 3), Hashimoto's thyroiditis (n = 1), hearing loss (n = 2), cholesteatoma (n = 3), and ear infection (n = 5), including otitis media. These low numbers likely reflect underreporting by investigators because these conditions are often nonserious and expected in patients with TS, and may be assessed as unrelated to rhGH.

Other serious events

Malignancies

There were 10 new-onset malignancies reported in NCGS patients with TS; three patients had medical histories that placed them at greater risk for malignancy development compared with the general population, *e.g.* gonadoblastoma with a 45X/46XY

TABLE 2. New-onset malignancies in GH-treated patients with TS and without prior risk factors

Patient age (yr)	AE	GH exposure (yr)	Treatment/outcome
16	Metastatic angiosarcoma of the liver	4	Expired
7	Papillary thyroid carcinoma	2	Thyroidectomy
10	Pineoblastoma	2	Biopsy
13	Wilms tumor	5	Surgical resection; no horseshoe kidney
13	Cerebral tumor, type not specified	3	Surgical resection
12	Osteogenic sarcoma of the femur	3	Surgery, chemotherapy

karyotype (10): chondrosarcoma of the same histological type as a fibrosarcoma, which occurred before GH therapy; and a mucoepidermoid carcinoma of the mouth in a TS patient with spina bifida (11). In addition, a patient with a prior diagnosis of focal nodular hyperplasia of the liver was found to have hepatocarcinoma 6 yr after the start of rhGH therapy. Table 2 summarizes the details of the malignancies in the six remaining patients with TS who did not have risk factors. A Wilms tumor was included in this nonrisk-factor group because the patient did not have a horseshoe kidney (a putative risk factor for Wilms tumor) (12). Table 3 compares the incidence of new-onset malignancies in TS patients without prior risk factors to the background malignancy rates in the age-matched general population. The SIR (observed/expected) was 2.1 (95% CI 0.76, 4.49).

In the non-TS NCGS population, the incidence of new onset malignancies in patients without risk factors (i.e. prior malignancy, radiation exposure, chemotherapy, bone marrow transplant, certain chromosomal disorders and congenital anomalies, and immunosuppressant therapies) was 0.06% compared to 0.11% for TS.

Table 4 lists other SAEs occurring in two or more TS patients. The remaining SAEs were single events that did not follow any particular pattern.

TABLE 4. Other SAEs occurring in two or more patients with TS enrolled in the NCGS

SAE	No. of reports
Bone fracture	5
Crohn's/inflammatory bowel disease	2
Focal nodular hyperplasia/hepatic adenoma	2
Injection device failure (needle breakage)[a]	2
Kyphosis	2
Nevus[b]	2

[a] Needle broke off in tissue of both patients, thereby listed as a SAE.

[b] One darkened and enlarged; one did not change from baseline but was surgically removed, thereby listed as a SAE.

Discussion

The NCGS database, established in 1985 at the time of the first introduction of biosynthetic GH, has grown to its current size of nearly 55,000 children treated with Genentech's GH products and has been used to assess safety issues over these years (13–16). This database contains baseline and treatment information for 5220 girls with TS, representing the largest registry of TS patients in the United States. We estimate, based on U.S. population statistics (17) and genetic data suggesting that the occurrence of TS is approximately one of 2500 live female births (1), that the number of TS patients entered into the NCGS in these 20 yr represents, conservatively, approximately 20% of all children and adolescents age 3–15 yr with TS in the United States during that interval. Thus, this analysis provides a unique opportunity not only to evaluate the safety of GH in these treated patients but also to try to determine what interactions GH might have with the underlying organic medical conditions/predispositions these patients exhibit, as well as to potentially obtain insights into the true epidemiology of medical events in this pediatric and adolescent age TS group that have not been previously captured in smaller epidemiological series unrelated to GH treatment (4, 18, 19).

With this context in mind, we examined the data in four categories: overall AEs, including deaths; targeted AEs known to be associated with or exacerbated by GH therapy, including IH, SCFE, scoliosis, pancreatitis, and diabetes; AEs that occur in increased frequency in TS, including cardiac, aortic and other vascular events, autoimmune disorders, and ear disorders; and other events, such as malignancy, in which the relationship with GH and TS is still unknown. The cutoff dates for AE data were slightly different between the TS and non-TS NCGS populations (June 30, 2006, and January 1, 2006, respectively) However, the increase in total NCGS enrollment was only 2.8% between January and June 2006, and this difference is unlikely to be clinically meaningful.

Overall AEs and deaths

The frequency of the overall AEs reported, 442 (8.5%), was slightly higher than among the rest of the patients in the NCGS (7.3%), likely reflecting the inherent complexity of the syndrome itself. No new safety signals emerged that were not otherwise associated with either GH or TS. SAEs were similar in frequency to those reported in the overall NCGS database. However, the occurrence of death was clustered into a category specific to TS. Five of the seven deaths recorded were related to aortic dissection or rupture, whereas there were no cases of this event occurring among the 167 deaths in the remainder of the NCGS.

Although the lack of this event in other patients in the NCGS and the known risk for aortic dissection in untreated TS patients suggest that GH is unlikely to be the precipitating factor, vali-

TABLE 3. New-onset malignancies in TS patients without risk factors *vs.* background malignancy rate in the general population

Patient age (yr)	NCGS years of GH exposure	Expected rate/100,000	Observed cases	Expected cases
0–4	842	20.4	0	0.17
5–9	5,456	11.4	1	0.62
10–14	10,990	12.9	4	1.42
15–19	3,436	20.0	1	0.69
20–24	29	34.9	0	0.01
Total	20,753		6	2.91

SIR (observed/expected) = 2.1 (95% CI 0.76, 4.49).

dated epidemiological data are lacking. The largest epidemiological studies of morbidity and mortality in TS are the nationwide studies of Gravholt and colleagues (18, 20) from Denmark, which included data from 781 living and 69 deceased TS women studied during 1970–2001. Despite low numbers of enrollees in the pediatric age group and of deaths from aortic rupture, their study of aortic dissection in all Danish patients estimated that 1.4 in 100 females with TS would suffer from aortic dissection over their lifetime, with occurrence at a strikingly young age, with an estimated incidence of dissection of 14 of 100,000 TS years in the 0–19 age group (21). This is consistent with the calculations made by Lin *et al.* (2), based on a questionnaire to members of the U.S. Turner Syndrome Society and a review of the literature, that 1.5% of children and women with TS would suffer from aortic dilation, and be at risk for dissection and rupture over their lifetime. If we exclude the patient who had an aortic dilation procedure for coarctation and ruptured and died in the postoperative period, four deaths within approximately 21,000 patient years would translate into approximately 19 of 100,000 patient years, which is generally consistent with the calculations in the young Danish population and the estimates by Lin *et al.*

Therefore, it is difficult to define the role, if any, of GH therapy in the cardiac events described. Echocardiographic studies in rhGH-treated girls with TS have shown normal ventricular morphology and function during and at cessation of therapy (22, 23), and several years thereafter (24). In a follow-up of one of these studies (23), magnetic resonance imaging performed at 6 months after rhGH cessation showed some degree of aortic dilation and impaired distensibility (25). The impaired distensibility was inversely related to the rhGH dose, suggesting an intrinsic abnormality upon which increasing doses of GH may have had a beneficial effect. Another study used magnetic resonance imaging in adult women, comparing those who were previously treated with GH to those who never received GH, and concluded that GH treatment did not affect aortic diameter above the increase that was related to body size (26). Thus, any relationship of rhGH to aortic pathology and specifically to aortic dissection and rupture remains speculative but unlikely. A more likely explanation is that aortic dissection and rupture are inherent to TS as a result of an as yet undefined vascular abnormality, and the number of affected patients in the NCGS relative to the very large number of TS patients in the NCGS reflects the underlying risk in the syndrome.

Of the remaining two deaths, one was an aspiration in a child with a neurological handicap, and one was a malignancy, which will be discussed subsequently.

Targeted AEs associated with or exacerbated by rhGH: IH, SCFE, scoliosis, pancreatitis, and DM

In the category of events known to be associated with GH therapy, a clear excess of these events occurred in patients with TS compared with the other categories in the NCGS. There were 12 cases of IH or pseudotumor cerebri reported, with a 0.25% frequency compared with a 0.12% frequency in the rest of the NCGS. Based on data that suggest the annual incidence in women in the age group 18–44 yr (youngest available) is 3.5 cases per 100,000 women per year (27), the 21,000 TS years would be approximately one case. Thus, our 12 cases are a 12-time excess. Although IH is known to be associated with GH therapy, and reported from the NCGS (28), a precise mechanism has not been defined. However, its occurrence appears to be greatest after rhGH treatment in those groups of patients at higher risk in the untreated state as well. That this may be true of patients with TS is suggested by two previous case reports (29, 30). Patients with CRI also have had an increased risk of IH independent of rhGH therapy (31) and have had the highest incidence in the NCGS database (twice the incidence of that reported in TS patients). Thus, it appears that although rhGH is associated with IH, this effect may be exaggerated in those predisposed to this condition.

SCFE is also known to be associated with rhGH therapy, and its occurrence in the NCGS has been reviewed previously (32). However, SCFE is also associated with obesity (33), endocrine conditions that affect growth in the untreated state, such as hypothyroidism and untreated GHD (34), and growth during puberty (35). The 2-fold greater frequency of SCFE in rhGH-treated TS children *vs.* other etiologies could be partially related to an increase in obesity in TS (progressing, in the NCGS, from 12–20% above the 95th centile for body mass index in the last 20 yr). This exceeds the Centers for Disease Control estimate for a similar pediatric population age group (36) and is greater than all other NCGS groups, except those females with organic GHD, over the same period (data on file). The higher rate of SCFE also suggests an intrinsic predisposition to orthopedic deformities that may be associated with their genetic chondrodystrophy secondary to SHOX (short stature homeobox containing gene on the X) haploinsufficiency (37). This is supported by the finding that five other TS girls in the NCGS had SCFE before GH initiation (0.1% of TS patients compared with 0.05% in the rest of NCGS).

Scoliosis is also common in untreated girls with TS (38–40). Although TS patients demonstrate a higher incidence of scoliosis reported as AEs than the other groups in the NCGS, the difference is not as great as might be expected, based on reports in untreated TS patients and may reflect underreporting. However, progression of scoliosis may be more rapid than anticipated, as reported in non-TS patients receiving rhGH treatment (41). Thus, although patients with TS are predisposed to scoliosis, rhGH treatment does not appear to contribute to an increased incidence but may accelerate progression. Therefore, care should be taken in monitoring these patients during therapy.

Pancreatitis was first associated with rhGH therapy in 1995, when 11 cases were known to the Food and Drug Administration (42), two involving girls with TS. Currently, in the NCGS there are three reports in TS (these are not included in the Food and Drug Administration report), and six in all other diagnoses. The CI approaches statistical significance and strongly suggests that TS patients are at higher risk for pancreatitis than other groups treated with rhGH. A mechanism linking pancreatitis with rhGH or the underlying disorders has not been described. However, several of the non-TS cases, including a most recently reported case with a coexisting mitochondrial cytopathy (43), display an underlying pathology that might predispose to the development of pancreatitis (pseudohypoparathyroidism, valproate therapy,

diabetes). Together, this information supports a recommendation for prompt evaluation of unexplained abdominal pain in girls with TS who are receiving rhGH treatment.

Reports of carbohydrate intolerance and DM in patients with TS date back to the early report by Forbes and Engle in 1963 (44). Since then, numerous studies and reviews have attempted, without success, to identify a single characteristic profile describing these abnormalities. In part, this research has been confounded by estrogen/progesterone status and replacement therapies, inability to assess body weight contributions in very short individuals, and lack of adequately matched controls to account for these variables. Whereas one report suggests that when controlled for variables of ovarian status and body mass, insulin secretion may be impaired in these patients (45), another report implicates first-phase insulin release as being abnormal with insulin sensitivity maintained (46), and still other data suggest resistance that appears to be intrinsic (47). Thus, although epidemiological data in adult TS patients not treated with GH show progression to a high prevalence of clinically significant types of carbohydrate abnormality (18), the underlying mechanisms remain unclear. Finally, the issue in children treated with GH may be confounded by what appears to be an increased incidence of type 1 diabetes due to the predisposition to autoimmune disorders characteristic of TS. Thus NCGS TS patients display an increased incidence of type 1 DM compared to the rest of NCGS and to the general pediatric population, and rhGH therapy may play a precipitating rather than an etiological role. It is also unclear how to interpret the other cases of "diabetes" not labeled by the physicians as type 1, given what appears to be a true increase in type 2 diabetes in childhood and no consensus to date on all the intrinsic abnormalities involved.

AEs occurring with increased frequency in TS patients, other: malignancies and other events

The development of *de novo* malignancies in rhGH-treated children, either during treatment or after cessation, has been difficult to address given the complex medical diagnoses and high degree of risk factors, as well as the lack of specific epidemiological data for their specific disorders. A retrospective analysis of a British cohort of largely GH-deficient children treated primarily with human pituitary GH and reassessed after an average of 16 yr after completion of GH therapy found an increased standardized mortality rate for colorectal cancer and Hodgkin's disease based on two cases of each (48). Cases occurring during the years of treatment were not reported. Conversely, the initial data suggesting an increase in leukemia during GH treatment (49) have not been confirmed over the next 15 yr (50) and have not been observed in NCGS children without risk factors (data on file, Genentech, Inc.). However, in children with prior malignancies, especially those of the central nervous system treated with irradiation, there appears to be an increased risk for the development of a second malignancy in those treated with GH compared with those not treated (51); however, a decline in the absolute difference over time compared with those not treated with GH may suggest facilitation of growth rather than direct causality (52). Although overall malignancies have been looked at in previous NCGS papers (13, 15), a subanalysis of TS patients has not been performed.

The SIR for *de novo* malignancies in the TS cohort is increased numerically relative to the background malignancy rate of the general population, and to the rest of the patients in the NCGS without known risk factors, although the CI is large and crosses one, indicating a lack of statistical significance. However, it is suggestive of either a relationship to rhGH or a reflection of predisposition of the underlying TS condition. The malignancies described are of diverse types and did not follow any particular pattern. In addition, incidence rates for the untreated TS population in this age range are not known. These data may reflect a slight predisposition to a variety of malignancies as a consequence of aneuploidy or an as yet undefined genetic mechanism.

Many other comorbidities may occur in patients with TS, including the spectrum of otological disorders from otitis media and cholesteatoma, to both conductive and sensory neural hearing loss, hypertension, urinary tract abnormalities and infection, thyroid disorders, and cognitive or psychiatric disorders. These events, although clinically important, were not consistently reported by NCGS investigators because they are often nonserious, and assessed as related to TS and not rhGH. Therefore, no further analyses of these conditions were performed based on NCGS data.

Conclusions

Pediatric and adolescent patients with TS appear to be at increased risk for some AEs associated with rhGH therapy, including IH, scoliosis, pancreatitis, and SCFE, compared with other rhGH populations. They are also at risk for events known to be associated with TS, including autoimmune disorders, and likely type 1 diabetes, as well as aortic dissection and rupture. Because there are no epidemiological databases for TS patients in this pediatric and adolescent age group of a magnitude sufficient to calculate risks for these conditions in untreated patients, the role of GH *vs*. the true background rates cannot be distinguished. Nevertheless, it is highly likely that the NCGS data are providing a window into the spectrum of many conditions that may be increased in TS in this age group, independent of a relationship to rhGH. Thus, guidelines for optimizing medical care of patients with TS, regardless of rhGH treatment and age, now include vigilance for aortic dissection and rupture, as well as for the other disorders known or possibly increased in TS (53, 54).

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