Original Paper

HORMONE RESEARCH

Horm Res 2009;71:52–59
DOI: 10.1159/000173742

Received: January 11, 2008
Accepted: April 19, 2008
Published online: November 27, 2008

European Multicentre Study in Children Born Small for Gestational Age with Persistent Short Stature: Comparison of Continuous and Discontinuous Growth Hormone Treatment Regimens

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Key Words
Small for gestational age · Growth hormone · Short stature

Abstract
Background: The most effective growth hormone (GH) treatment regimen for increasing height in short children born small for gestational age (SGA) has not been well defined. ***Methods:*** Short SGA children (n = 151, age 3–8 years, height less than –2.5 standard deviation scores) were randomised to receive low-dose GH for 2 years (0.033/0.033 mg/kg/day, n = 51), high-dose GH for 1 year and then no treatment for 1 year (0.100/0 mg/kg/day, n = 51) or were untreated for 1 year then received mid-dose GH for 1 year (0/0.067 mg/kg/day, n = 47). Height, bone age and adverse events were determined at check-ups every 3 months. ***Results:*** The mean ± SD additional height gain with GH after 1 year, relative to untreated controls, was higher with discontinuous high-dose than with continuous low-dose GH (6.5 ± 0.2 vs. 3.3 ± 0.2 cm). After 2 years, the additional height gain was similar between high- and low-dose GH groups (between-group treatment difference = 0.2, 95% CI = –0.8 to 1.2 cm, p = 0.702). Patients treated exclusively in the last year had a similar height gain to those in the other treatment groups (p = 0.604). ***Conclusions:*** In short SGA children, continuous low-dose and discontinuous high-dose GH regimens were associated with similar height gain. Treatment with mid-dose GH for 1 year also led to a similar improvement in growth.

Introduction

Approximately 5% of children are born small for gestational age (SGA, defined as birthweight/birth length less than –2 standard deviation scores, SDS) [1]. Most SGA infants experience a period of accelerated growth during the first 12 months of life that results in a nor-

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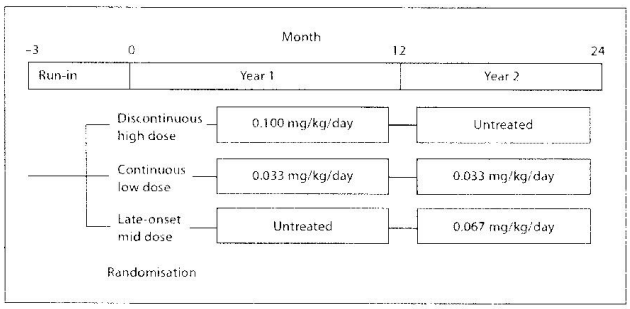

Fig. 1. Study design.

malisation of height in up to 90% of them [2]. Most of this catch-up growth occurs during the first year and is near to completion by 2 years of age [1, 2]. SGA infants who do not experience spontaneous catch-up growth remain short during childhood and eventually achieve adult heights that are usually below –2 SDS [1, 3]. Previous studies suggest that this cohort of adults who were born SGA and who have persistent growth retardation comprise 20% of the total population of short-statured adults [1].

In children who remain short after 2 years of age, treatment with recombinant human growth hormone (GH) at doses of 0.033–0.067 mg/kg/day is associated with a significant acceleration of linear growth, resulting in a height within the normal range during childhood [4–7]. In short- and mid-term studies, height gains range from 1.1 to 2.6 SDS depending on the age of the child at the start of treatment, the GH dosage and the duration of GH therapy [5, 8–13]. After the initial catch-up, most of this height gain is maintained, allowing the majority of children to achieve an adult height within the normal range for their population [14]. During the early years of treatment, a dose-response relationship between height gain and GH dose (0.033–0.067 mg/kg/day) has been described, with increases being significantly greater in those receiving 0.067 mg/kg/day than in those receiving 0.033 mg/kg/day [5, 10]. Current recommendations support the use of higher GH doses in those children with the most marked growth retardation [15, 16]. However, the optimal GH dose regimen remains a matter for debate, with some authors preferring continuous treatment [5] and others favouring discontinuous treatment [10]. In a small cohort of short-statured SGA children, preliminary data showed that a similar gain in height was achieved with the use of high-dose GH (0.100 mg/kg/day) for a period of 2 years as compared with continuous low-dose GH for up to 6 years [15]. However, a marked catch-down in growth has been reported following discontinuation of GH treatment, especially during the first off-treatment year [11, 16, 17].

The aim of the present study was to compare the gain in height over 2 years in short SGA children receiving 3 different GH treatment regimens.

Patients and Methods

Study Design and Patients

This was a multinational, 2-year, randomised, prospective, parallel group study comparing the efficacy and safety of three different dose regimens of recombinant human GH (Norditropin®, Novo Nordisk A/S, Bagsværd, Denmark). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments, and local ethical committee or institutional review board approval was obtained at each study centre. Informed consent was signed by the parent or guardian of each child included in the study.

The study population comprised treatment-naïve children 3–8 years of age, who had persistent short stature and who were born SGA (birth weight and/or length ≤–2 SDS), a height SDS ≤–2.5 SDS, a height velocity SDS ≤0 during the last 3 months before study entry, a parental height ≥–2 SDS of their population's mean, and a normal response to a GH stimulation test [peak ≥10 ng/ml (20 mIU/ml)]. Patients entered the study in a 3-month run-in period during which eligibility was assessed and prestudy height was measured. Patients were then randomised 1:1 to double-blind treatment in the two active GH treatment groups or to a control group that was untreated in the first year and started GH treatment in the second year (fig. 1). A computer-controlled, centralised (at Novo Nordisk A/S) system was used to assign treatment. The study extended from November 2002 (first visit of the first patient) to July 2006 (last visit of the last patient).

Table 1. Patient characteristics at birth and at baseline

	Continuous low-dose GH (0.033/0.033 mg/kg/day) (n = 51)	Discontinuous high-dose GH (0.100/0 mg/kg/day) (n = 51)	Mid-dose GH (0/0.067 mg/kg/day) (n = 47)
M:F, %	55:45	47:53	51:49
Birth length, cm	44.3 ± 5.3	44.6 ± 4.3	43.9 ± 5.0
Birth weight, kg	1.9 ± 0.6	2.0 ± 0.6	2.0 ± 0.6
Gestational age, weeks	36.9 ± 3.6	37.6 ± 3.3	37.5 ± 3.2
Target height SDS	−0.9 ± 0.6	−0.8 ± 0.6	−0.9 ± 0.8
Height, cm	99.0 ± 9.3	98.9 ± 9.0	99.2 ± 7.9
Height SDS	−3.1 ± 0.5	−3.2 ± 0.7	−3.1 ± 0.5
Age, years	5.5 ± 1.5	5.5 ± 1.4	5.6 ± 1.4
Bone age, years	4.7 ± 1.8	4.9 ± 1.8	5.0 ± 1.9
BA:CA	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2

Data are means ± SD, unless otherwise stated. BA:CA = bone age-to-chronological age ratio.

During the first study year, patients in the continuous low-dose group received GH at a daily dose of 0.033 mg/kg, and those in the discontinuous high-dose group received GH at a daily dose of 0.100 mg/kg, while the control group were untreated (fig. 1). At the end of the first year, patients in the continuous low-dose group continued treatment and those in the discontinuous high-dose group stopped treatment. Patients in the untreated control group received GH at a daily dose of 0.067 mg/kg in the second year of the study. An untreated control group was selected in year 1 because placebo therapy was considered unethical. GH was administered as a daily subcutaneous injection using a pen injection device (NordiPen®, Novo Nordisk A/S).

Patients in the continuous low-dose or discontinuous high-dose treatment groups had clinical assessments at 1.5, 3, 4.5, 6, 9, 12, 15, 18, 21 and 24 months after randomisation. Patients randomised to the untreated group in the first year had additional visits at 13.5 and 16.5 months after starting GH treatment months (1.5 and 4.5 months after starting treatment with GH 0.067 mg/kg/day). At each visit, height was recorded as the mean of 4 independent observations using a Harpenden stadiometer (Holtain Ltd., Crymych, UK). The target height for boys was calculated from the mean height of the parents plus half the difference between the means of the male and female populations. The target height for girls was calculated as mean height of parents minus half the difference between the means of the male and female populations. Sex-adjusted target height was then calculated based on appropriate national height references. Bone age (BA, TW2-RUS) [18] was assessed centrally using X-ray by clinicians who were blinded to the subject's characteristics and treatment (except for gender). Body weight (in kg) was assessed at each visit. Safety was also assessed by recording the occurrence of adverse events during the trial.

Study Assessments

The primary endpoint of the study was measurement of height during 2 years of treatment. The treatment effect was measured as the additional height gain with GH above that in the untreated short SGA children during the first year of the study. Secondary endpoints included height SDS after each year of treatment, change in insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels during treatment, as well as changes in fasting glucose, insulin and glycosylated haemoglobin (HbA_{1c}) levels. Height SDS was calculated according to the appropriate population references by country. IGF-1 and IGFBP-3 concentrations were converted to SDS values by comparison with data from a healthy reference population.

Measurements of IGF-I and IGFBP-3, glucose, insulin and HbA_{1c} were performed centrally at the Laboratorium für klinische Forschung, Raisdorf, Germany.

Statistical Analyses

Statistical analysis of additional height gain, as well as other efficacy variables, was performed using a mixed effects model (ANCOVA) where effects of age, sex and treatment duration were included. The effects of age and treatment duration were assumed to be piecewise linear within each year. Height gain of the untreated children during the first year of the study was used as a reference for untreated children. The subjects' individual starting heights and yearly growth rates were included as random effects. All tests were 2-sided F tests, performed at the 5% level of significance.

With a randomisation ratio of 1:1, at least 50 patients had to be enrolled in each group to detect a difference in height gain of 0.75 cm between continuous and discontinuous treatment groups with a power of 90% and a significance level of 0.05. To allow comparisons of secondary objectives with the third treatment group, as well allowing for a study dropout rate of 20%, 180 subjects were required to be enrolled in the study. A total of 151 patients were randomised in the study, 51 received continuous low-dose GH (0.033/0.033 mg/kg/day), 51 received discontinuous high-dose GH (0.100/0 mg/kg/day) and 45 were untreated in Year 1 and received mid-dose GH (0/0.067 mg/kg/day) in Year 2. All were available for the determination of safety and 149 (n = 51, n = 51, n = 47) were available for the efficacy analysis.

Results

Patient Demographics

Baseline demographic data are shown in table 1. All patients were prepubertal and there were no differences between treatment groups in chronological age (CA), bone age (BA), gender distribution and auxological data.

Efficacy

Additional Height Gain. Additional height gain was defined as that above the height gain in the untreated SGA children during the first year of the study, that is, those randomised to the 0/0.067 mg/kg/day group. After 2 years mean ± SD additional height gain was comparable between the continuous low-dose (4.9 ± 0.5 cm) and discontinuous high-dose (5.1 ± 0.4 cm) treatment groups (estimated between treatment difference = 0.2,

Table 2. Actual height (cm) and gain in actual height (cm) from baseline by treatment group and by study duration

	GH dose		
	0.033/0.033 mg/kg/day (n = 51)	0.100/0 mg/kg/day (n = 51)	0/0.067 mg/kg/day (n = 47)
Height SDS			
Height SDS at baseline	−3.1 ± 0.5	−3.2 ± 0.7	−3.1 ± 0.5
Height SDS at end of Year 1	−2.3 ± 0.6	−1.8 ± 0.8	−3.0 ± 0.6
Height SDS at end of Year 2	−2.0 ± 0.6	−2.0 ± 0.9	−2.1 ± 0.8
Change in height SDS			
Change in height SDS during Year 1	0.8 ± 0.3	1.4 ± 0.4	0.1 ± 0.3
Change in height SDS during Year 2	0.3 ± 0.2	−0.2 ± 0.2	1.0 ± 0.4
Overall change in height SDS from baseline to end of study (Year 1+Year 2)	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.5

Data are means ± SD.

95% CI = −0.8 to 1.2, p = 0.702). During the first study year mean (± SD) additional height gain with GH therapy was greater in the discontinuous high-dose group than in the continuous low-dose group (6.5 ± 0.2 vs. 3.3 ± 0.2 cm; fig. 2). The between-treatment difference at 1 year was not evaluated statistically.

In the second study year, patients in the discontinuous high-dose group experienced a catch-down in growth after stopping treatment and gained less height than expected; that is, additional height gain was less than in the untreated children in Year 1 (mean ± SD = −1.4 ± 0.3 cm, 95% CI = −2.0 to −0.8 cm; fig. 2). For patients in the mid-dose group, the additional height gain following GH treatment in Year 2 (5.1 ± 0.2 cm) was not significantly different from height gain at 2 years in the other GH treatment groups (p = 0.604; fig. 2).

Additional height gain during the first year of treatment was dose-dependent with the greatest additional height gain in the discontinuous high-dose group (low-dose Year 1: estimated mean = 3.3 cm, 95% CI = 2.9–3.7 cm; high-dose Year 1: estimated mean = 6.5 cm, 95% CI = 6.0–6.9 cm; mid-dose Year 2: estimated mean 5.1 cm, 95% CI 4.7–5.6 cm; p < 0.0001).

Height SDS. During the first study year, the mean gain in height SDS was greatest in the discontinuous high-dose group (table 2). After 2 years the mean increase in height SDS was not different between treatment groups (table 2). Indeed, a similar proportion of patients across treatment groups had achieved a height within the normal population range (more than −2 SDS) after 2 years.

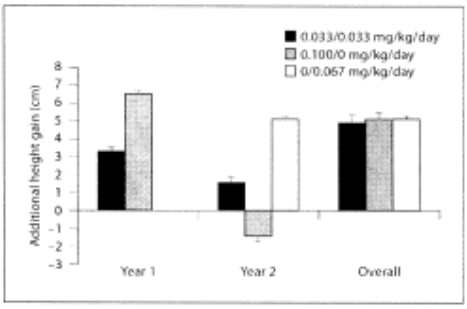

Fig. 2. Additional height gain in each treatment group in the first and second years of the study and over the 2-year study period. Additional height gain is the additional estimated gain in height after GH treatment. Gain in height in the untreated group during the first year of the study is, therefore, not shown. Data are mean ± SD.

Safety

Adverse Events. GH treatment was well tolerated in all dosage groups. Adverse events were reported in 61% of children in the continuous low-dose group, compared to 67% in the discontinuous high-dose treatment group and 71% in the mid-dose group. The majority (349/358, 73.5%) of adverse events were mild to moderate in severity, and the most common events (57%) were childhood infections. Sixteen serious adverse events were noted, 3 of

Table 3. Changes in serum concentrations and IGF-I SDS by treatment group from baseline to end of Year 1 and end of Year 2

	GH dose, mg/kg/day		
	0.033/0.033 (n = 51)	0.100/0 (n = 51)	0/0.067 (n = 51)
IGF-I, ng/ml			
Baseline	116.7 ± 59.4	145.9 ± 92.3	130.0 ± 84.1
End of Year 1	345.6 ± 177	594.3 ± 221	176.3 ± 107
End of Year 2	366.7 ± 206	222.5 ± 106	569.5 ± 273
IGFBP-3, µg/l			
Baseline	3.2 ± 0.9	3.5 ± 0.9	3.4 ± 1.1
End of Year 1	4.8 ± 1.1	6.1 ± 1.4	3.9 ± 1.1
End of Year 2	5.0 ± 1.2	4.4 ± 1.2	5.8 ± 1.2
IGF-I SDS			
Baseline	−1.4 ± 0.6	−1.1 ± 0.9	−1.2 ± 1.0
End of Year 1	0.9 ± 1.9	3.3 ± 2.1	−0.9 ± 1.2
End of Year 2	0.8 ± 2.1	−0.6 ± 1.0	2.9 ± 2.8
Fasting glucose, mmol/l			
Baseline	4.6 ± 0.6	4.7 ± 0.6	4.6 ± 0.4
End of Year 1	4.8 ± 0.5	5.0 ± 0.5	4.8 ± 0.6
End of Year 2	4.8 ± 0.4	4.6 ± 0.4	4.8 ± 0.6
Fasting insulin, µIU/ml			
Baseline	3.1 ± 2.8	2.7 ± 1.9	2.8 ± 3.3
End of Year 1	5.3 ± 3.5	8.9 ± 5.0	4.1 ± 6.3
End of Year 2	6.3 ± 4.7	4.3 ± 2.9	8.2 ± 5.4
HbA_{1c}, %			
Baseline	5.2 ± 0.4	5.2 ± 0.3	5.1 ± 0.4
End of Year 1	5.3 ± 0.4	5.3 ± 0.2	5.2 ± 0.4
End of Year 2	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.4

Data are means ± SD.

which were likely to be related to GH therapy (in the 100/0 mg/kg/day group 1 patient reported convulsions and epilepsy, in the 0/0.067 mg/kg/day group 1 patient developed papilloedema). GH was discontinued temporarily in both cases, after which both patients made a full recovery or, in the case of epilepsy, the condition stabilised.

Bone Age. The mean BA:CA ratio was 0.8 ± 0.2 across treatment groups at baseline and normalised to a value of 1.0 in all treatment groups at 2 years.

IFG-I and IGFBP-3. Serum concentrations of IGF-I and IGFBP-3 and the IGF-I SDS are shown in table 3. Both concentrations and the SDS increased from baseline to Year 2 with GH treatment. On stopping GH treatment, levels of these parameters decreased and returned to near to baseline values. Mean IGF-I SDS was outside the normal reference range (−2 to 2 SDS) at 2 years in the discontinuous high-dose group and after 1 year in the mid-dose group.

Fasting Glucose, Insulin and HbA_{1c} Levels. Mean fasting glucose levels increased during GH treatment (table 3). Discontinuation of GH treatment in the discontinuous high-dose group during Year 2 was associated with a reduction in mean fasting glucose levels below pre-study levels (table 3). Insulin levels also increased (within the reference range of 2.6–24.9 µIU/ml) during periods of GH treatment (table 3). In Year 2, stopping GH treatment in the high-dose GH group led to a reduction in insulin levels. No clinically relevant changes in HbA_{1c} were observed during the treatment period (table 3). Two non-serious adverse events were related to glucose metabolism. In the low-dose continuous GH group HbA_{1c} levels increased to above the reference range in 1 patient, and in the discontinuous high-dose GH group hyperglycaemia was reported in 1 patient.

Discussion

In the present study, GH treatment for 2 years improved height gain in severely growth-retarded children born SGA. After 2 years, the height gain was not different between the continuous low-dose and the discontinuous high-dose GH regimens. The gains in height after 2 years' continuous GH therapy reported in this study are consistent with those described in studies in which a similar GH dosage was used [5, 10]. The results in the discontinuous treatment arms in our study are in agreement with findings from other studies comparing discontinuous and continuous treatment regimens [10, 19].

In our study, catch-down growth was observed following discontinuation of GH in the high-dose group. This was, however, of limited magnitude compared to the overall height gain during the study. Other authors have reported a reduction in height velocity [13] or mean loss in the height SDS [11, 17] in SGA children after stopping GH treatment. Interestingly, the mean gain in overall height in our study was not different for patients in the mid-dose GH group who started GH after 1 year and the group on the continuous low-dose regimen.

In the present study approximately half of the children in each treatment group achieved a stature above −2 SDS after 2 years.

Consistent with other published reports on the efficacy of GH in prepubertal SGA children [5, 7, 10, 16, 20, 21] we found a dose-dependent height gain during the first treatment year. Similar to findings in other studies involving girls with Turner syndrome and in GH-defi-

cient patients, as well as in patients born SGA, we found that height gain during the first treatment year was higher than that in the second treatment year for patients in the continuous GH group [6, 22–25]. This phenomenon may be multifactorial, including reduced responsiveness of the growth plate to GH and/or IGF-I with long-term exposure [26].

In the present study, GH was not associated with any new or unknown considerations regarding the safety of GH in a paediatric population. Of the 3 serious adverse events that were considered possibly related to the action of GH, the epilepsy occurred in a patient with a medical history of cerebral haemorrhage. A possible sequela of cerebral haemorrhage is development of epilepsy [27]. In the case of papilloedema no evidence of benign intracranial hypertension could be verified (using computerised tomography and magnetic resonance imaging scans), although a causal relationship to GH treatment could not be excluded. As in other studies, we found that GH treatment was associated with a dose-dependent increase in both IGF-I and IGFBP-3 levels [21, 28]. No clinically adverse disturbance in glucose metabolism was observed either during GH treatment or during the follow-up period. In accordance with other reports [32–35], although fasting glucose levels and insulin levels increased during the treatment period, these changes appeared to be reversible on cessation of GH treatment. Changes in insulin-to-glucose ratios have been reported in other studies, but in most patients the impaired glucose tolerance may be transient and the glucose tolerance is not altered.

BA was delayed relative to CA at baseline but advanced during GH treatment, resulting in a normalisation of the BA:CA ratio at 2 years. Similar data describing BA progression during GH treatment from low baseline levels [18, 36, 37] have been reported by other authors.

In conclusion, continuous low-dose and discontinuous high-dose regimens of GH administration result in a similar increase in height SDS after 2 years. Discontinuation of GH in the high-dose group for 1 year was followed by catch-down in growth resulting in a total height gain during that year that was below the predicted value. Our results also suggest that a mid- to high-dose GH treatment regimen provides a valuable treatment option for late starters of GH therapy.

Conflict of Interest Statement

Moshe Phillip received lecture fees and grant support (both paid direct to his institute) from the company that supported the study; Jan Lebl received consulting fees and lecture fees; Nehama Zuckerman-Levin received grant support; Adam Steensberg, Kirsten Jons, Anne-Marie Kappelgaard are employed by the company that supported the study; Yael Lebenthal, Maria Korpal-Szczyrska, Jorge Sales Marques, and Lourdes Ibanez have nothing to declare.

Acknowledgements

This study was sponsored by Novo Nordisk A/S. The authors are grateful to the following investigators and study sites who participated in the study. Leo Dunkel, Marita Lipsanen-Nyman, Ilkka Sipilä, Timo Otonkoski and Risto Lapatto, Helsinki, Raimo Voutilainen, Sirpa Tenhola, Ulla Sankilampi, Kuopio, and Päivi Tapanainen and Riitta Veijola, Oulu, Finland; Jirina Zapletalova, Olomouc, Dana Novotna, Brno, Jaroslav Skvor, Ústí nad Labem, and Jan Lebl, Stanislava Kolouskova and Bozena Kalvachova, Prague, Czech Republic; Ester Liberman, Eli Hershkovitz and Neta Loewenthal, Be'er Sheva, Moshe Phillip and Yael Lebenthal, Petach-Tikva, Zvi Zadik and Amnon Zang, Rehovot, and Ze'ev Hochberg, Nehama Zukerman-Levin and Dov Tiosano, Haifa, Israel; Tomasz Romer and Alicja Korpysz, Warsaw, Jerzy Starzyk, Agata Zygmunt Górska, Malgorzata Kumorowicz-Kopiec, Dominika Januś, Dorota Roztoczyńska, Anna Kalicka-Kasperczyk, Aleksandra Górska, Katarzyna Doleżal-Oltarzewska, Dorota Bilecka and Edyta Piątkowska, Kraków, and Maria Korpal-Szczyrska, Bohdana Dorant, Halina Kamińska and Dorota Birkholz, Gdańsk, Poland; Eberhard Keller, Johannes Weigel, Alexandra Keller and Sabine Liebermann, Leipzig, Klaus-Peter Ullrich, Gotha, and Stefan Wirth and Philip Wintermeyer, Wuppertal, Germany; Manuel Jorge Fontoura Pinheiro de Magalhães and Cíntia Gonçalves Castro-Correia, Porto, Mario Aires Marcelo da Fonseca, Matosinhos, Luis Francisco Simões de Moura and Maria Alice Santos Cordeiro Mirante, Coimbra, and Jorge Manuel Sales Marques, Jacinto Américo Silva Torres, Rosa Arménia Martins Campos and Marta Vila Real Magalhães Coelho, Vila Nova de Gaia, Portugal; Jesús Argente Oliver, Jesús Pozo, Ricardo Gracia Bouthelier, Antonio Oliver Iguacel, Amparo Rodriguez Sánchez and Dolores Rodriguez Arnao, Madrid, Concepción Carles Genotes and Vicente Albiach, Valencia, Antonio Carrascosa Lezcano and Diego Yeste, Francisco Rodriguez-Hierro and Lourdes Ibanez, Barcelona, Juan Manuel Fernández Garcia and Carlos Ruiz, Granada, Juan Pedro López-Siguero, Maria José Martínez Aedo and Almudena del Pino, Malaga, and Manuel Pombo Arias and Jesús Barreiro Conde, Santiago de Compostela, Spain; Olle Söder and Eva Horemizová, Stockholm, Jan Åman, Örebro, and Mirek Vejvoda and Christian Penno, Helsingborg, Sweden.

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