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Research Article

# Safety and outcome of treatment with voriconazole in a large cohort of immunocompromised children and adolescents

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## Abstract

**Objectives:** Post-marketing data on safety and outcome of voriconazole (VCZ) treatment in pediatric patients is limited. We performed a retrospective, single center analysis of safety, tolerance and antifungal efficacy in a large cohort of children and adolescents requiring VCZ therapy.
**Patients and methods:** The cohort included 107 patients (0.2–18 years of age) with hematological disorders (85; 42 post allo-HSCT), primary immunodeficiencies (9), AIDS (4), metabolic diseases (5) and solid tumors (4) who received 252 courses of VCZ for possible (12) and probable/proven (25) invasive fungal diseases (IFDs), as primary (127) or secondary (79) prophylaxis or as empiric therapy (9). VCZ was given IV (10) and (37)/or (205) PO at recommended dosages until intolerance or maximum efficacy. IFDs and outcomes were assessed by EORTC/MSG consensus criteria.
**Results:** VCZ was administered at a median maintenance dosage of 5.9 mg/kg twice daily (range, 2.2–22.0) for a median of 65 days (range 1–1,002). While on treatment, increases in hepatic transaminases, serum bilirubin and alkaline phosphatase, skin eruptions and neurological adverse events (AEs) were observed in 53.5, 23.6, 10.9, 5.6 and 4.8% of courses, respectively. At end of treatment (EOT), mean alkaline phosphatase, aspartate aminotransferase and serum bilirubin values were slightly elevated relative to baseline ($p<0.01$). AEs prompting discontinuation of VCZ occurred in 18 courses (7.1%). Treatment success was observed in 16/37 patients with proven/probable/possible IFDs, and in 187/215 courses of empiric therapy and prophylaxis. Overall survival was 97.6% at EOT and 92.1% at 3 month post EOT, respectively.
**Conclusions:** VCZ displayed acceptable clinical safety and tolerance and was effective in the management of IFDs in severely immunocompromised children and adolescents.

**Keywords:** mycoses, children, cancer, voriconazole, safety

## Introduction

Opportunistic invasive fungal diseases (IFDs) are important infectious complications in severely immunocompromised pediatric patients and a cause of considerable morbidity and mortality [1]. Voriconazole is a second generation synthetic triazole with broad spectrum antifungal activity *in vitro* against most clinically relevant fungal pathogens [2]. The compound is available in oral and intravenous formulations and has demonstrated clinical efficacy and safety in adult phase III clinical trials of primary treatment of superficial and invasive candidiasis [3], [4], invasive aspergillosis [5] and for empirical therapy in persistently febrile neutropenic patients with cancer [6], and there is evidence for its effectiveness as antifungal prophylaxis in high risk patients [7], [8].
Voriconazole has approved first line indications against major opportunistic mycoses in subjects ≥12 years of age in both the United States and the European Union. The recommended intravenous dosage is 4 mg/kg BID (day 1: 6 mg/kg BID), and the oral dosage is 200 mg BID (Day 1: 400 mg BID) (<40 kg body weight: 100 mg BID with a loading dose of 200 mg BID on day 1). While the compound has been approved in the European Union in children at the age of ≥2 to 11 years since 2005, the dose finding in this age group has been difficult with several revisions in the recommended dosages. Currently, an intravenous dosage of 8 mg/kg BID (day 1: 9 mg/kg BID) and an oral dose of the suspension of 9 mg/kg BID has been adopted by the European Medicines Agency (EMA) for children at 2 to <12 years of age and at 12 to 14 years of age weighing <50 kg and these dosages are being further investigated in clinical phase II trials conducted by the manufacturer [9], [10].
Despite several years of regulatory approval and widespread use, post-marketing data on safety, tolerance and

outcome of voriconazole in children and adolescents still is limited [11], [12]. We therefore conducted a retrospective analysis of safety, tolerance and antifungal efficacy in a cohort of 107 consecutive immunocompromised children and adolescents receiving a total of 252 courses of voriconazole treatment at our center.

# Patients and methods

## Study design

The study was a single-center retrospective non-comparative cohort study of immunocompromised pediatric patients who were considered to require therapy with voriconazole and was conducted between October 2002 and January 2010 [13]. Patients eligible for inclusion in this analysis were ≤18 years of age and had received at least one day of treatment with voriconazole. Voriconazole was administered at recommended dosages [9] until occurrence of intolerance or maximum efficacy for treatment of presumed or documented invasive fungal diseases, as empiric therapy, or as primary or secondary antifungal prophylaxis. All patients received several concurrent therapies for management of their underlying diseases and their complications. Written informed consent for antifungal therapy as part of the medically indicated measures of supportive care and for data collection was obtained within the consent procedure for cancer treatment, hematopoietic stem cell transplantation (HSCT), and specialized medical care. Data collection was accomplished by a pseudonymized standardized case report form.

## Assessment of safety and tolerance

Independent of cause, laboratory parameters of hepatic and renal organ function were measured at baseline (BL) and at the end of treatment (EOT). In addition, the most pathological value during treatment was evaluated for each parameter and episode. Clinical and laboratory adverse events (AEs) were recorded and graded according to current Common Terminology Criteria of Adverse Events (CTCAE) set forth by the U.S. National Cancer Institute [14] in consideration of age-related reference values. A clinical AE attributable to voriconazole was defined as an event that was not present at BL but developed during the treatment and resolved completely after cessation of therapy.

## Assessment of antifungal efficacy

Coding of invasive fungal infections and outcome was performed by the investigators responsible for data analysis (AHG and SP) according to the 2008 EORTC/MSG criteria [15], [16]. A favorable response ('success') in patients with possible/probable/proven infections included either 'complete response' or 'partial response', and failure included 'stable disease' or progression or death due to the infection. For prophylaxis and empirical therapy, success was defined as completion of therapy without recurrent or breakthrough fungal infection, no discontinuation due to adverse events, and survival at the time of discontinuation of the compound [17]. For the purpose of correlating dose with efficacy, absence of recurrent or breakthrough infection during voriconazole prophylaxis/empirical therapy was graded as favorable response ('success').

## Statistical considerations

For statistical analyses, Predictive Analysis Software (PASW) version 18.0.0 was used. Comparisons of laboratory values during therapy were performed by the Wilcoxon signed rank test. Relationships between clinical or laboratory data and daily dose were analyzed by non-parametric Spearman correlation, the Mann-Whitney U test or by Kruskall Wallis ANOVA. A two-sided p-value of ≤0.05 was considered as statistically significant.

# Results

## Patients

During the seven-year observation period, a total of 252 separate courses of treatment with voriconazole were administered to 107 children and adolescents. Patients' demographic and clinical characteristics are summarized in Table 1. 62 of the 107 patients were male and 45 were female. Most were of Caucasian origin (91.6%), and the mean age at the initiation of antifungal therapy was 10.1 years (range 0.2 to 18 years). The overwhelming majority of patients had hematological malignancies (66.4%) or bone marrow failure syndromes (10.3%) as underlying condition; 39.3% were status post allogeneic HSCT.

## Indications and administration of voriconazole

Treatment indications and details of treatment with voriconazole are outlined in Table 2. Patients received voriconazole mostly for primary or secondary prophylaxis (127 and 79 of 252 courses, respectively (81.7%)). Voriconazole was administered as empirical therapy in 9, as treatment for possible IFDs in 12, and as treatment for probable or proven IFDs in 25 courses. Voriconazole was combined with other systemic antifungal agents in 13/37 courses for therapy of fungal infections. In 55.9% of the 252 treatment courses, treatment was initiated during granulocytopenia, and in 71.4 %, respectively, patients had been at least temporarily granulocytopenic while on treatment. The mean duration of granulocytopenia was 13.1 days (median: 10 days; range 2 to 67 days).
The mean duration of treatment with voriconazole was 65 days (range 6–1,002). The majority of patients (81.3%) received voriconazole orally; in 14.7% treatment was

**Table 1: Demographic and clinical characteristics in 107 patients with voriconazole**

| Characteristic | No. (%) of patients or mean value |
|---|---|
| *Demographic data:* | |
| age (years) | 10.1 (range 0.2–18) |
| <24 months | 7 |
| 2–12 years | 54 |
| >12 years | 46 |
| sex (male : female) | 62 (58) : 45 (42) |
| *Underlying conditions:* | |
| hematological malignancy | 71 (66.4) |
| bone marrow failure | 11 (10.3) |
| congenital immunodeficiency | 9 (8.4) |
| Acquired Immunodeficiency Syndrome | 4 (3.7) |
| non-neoplastic hematological disorder | 3 (2.8) |
| metabolic diseases | 5 (4.7) |
| solid tumor | 4 (3.7) |
| *Transplantation status:* | |
| allogeneic HSCT | 42 (39.3) |
| autologous HSCT | 1 (0.9) |
| syngenic HSCT | 1 (0.9) |
| *Comorbidities:* | |
| acute or chronic GvHD | 14 (13.1) |

HSCT: hematopoietic stem cell transplantation; ANC: absolute neutrophil count; GvHD: Graft-versus-Host-Disease

**Table 2: Treatment indications and details of treatment in 252 courses of voriconazole**

| Characteristics | No. (%) of courses or value |
|---|---|
| *Treatment indication:* | |
| primary/secondary prophylaxis | 206 (81.7) |
| empirical antifungal therapy | 9 (3.6) |
| possible invasive infections | 12 (4.8) |
| pulmonary mould infection | 9 |
| disseminated candidiasis (liver, spleen) | 3 |
| probable/proven invasive infections | 25 (9.9) |
| pulmonary aspergillosis | 12 |
| disseminated aspergillosis (CNS, lung, sinuses) | 3 |
| esophageal/ oral candidiasis | 3 |
| candidemia | 3 |
| *Paecilomyces* granuloma | 1 |
| pulmonary trichosporonosis | 1 |
| Curvularia sinusitis | 1 |
| catheter infection (aspergillosis) | 1 |
| *Absolute neutrophil count (ANC):* | |
| <500/uL at start of treatment | 141 (55.9) |
| <500/uL at any time during treatment | 180 (71.4) |
| Mean duration of ANC<500/uL [days] | 13.1 (range 2–67) |
| *Administration:* | |
| intravenous | 10 (4.0) |
| intravenous/by mouth | 37 (14.7) |
| by mouth | 205 (81.3) |
| Median maintenance dose [mg twice daily] | 177.0 (range 20–500) |
| Median maintenance dose [mg/kg twice daily] | 5.9 (range 2.2–22.0) |
| Mean duration of therapy [days] | 65 (range 6–1002) |

CNS: Central Nervous System

**Table 3: Laboratory adverse events during 252 courses of voriconazole tabulated according to the CTCAE classification**

| Grade of laboratory AEs | I–IV* | I | II | III | IV |
|---|---|---|---|---|---|
| | N (%) | | n | | |
| *ALT* | 116 (53.5) | 78 | 17 | 21 | 0 |
| *AST* | 98 (45.6) | 71 | 13 | 14 | 0 |
| *Bilirubin* | 51 (23.6) | 27 | 18 | 6 | 0 |
| *Alk. Phos.* | 21 (10.9) | 18 | 3 | 0 | 0 |
| *Creatinine* | 31 (14.1) | 19 | 12 | 0 | 0 |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Alk.Phos.: alkaline phosphatase

* Complete data available for ALT, AST, bilirubin, Alk. Phos., creatinine in 217, 215, 216, 192, 220, respectively, of 252 courses.

started intravenously and switched to oral, and in 4% of the courses, voriconazole was given by the intravenous route. The median maintenance dose was 177.0 mg twice daily (range 20–500), corresponding to 5.9 mg/kg of body weight twice daily (range 2.2–22.0; wide dose range explained by the fixed oral dose for children <12 years during the time of the study). Dosage modifications occurred in 55 courses because voriconazole trough concentrations were considered too low (14) or too high (2). Other reasons for dosage modifications were change of the application form (20), intolerance (4), or unknown (15).

## Safety and tolerance

Independent of causal relationship, AEs were observed in 167/252 courses. Increases in hepatic transaminases (54%), serum bilirubin (24%) and alkaline phosphatase (11%) while on treatment were frequent but mostly grade I or II (Table 3). Further attributable clinical AEs included skin eruptions (phototoxic erythema (9), exanthema (5)), neurological symptoms (photophobia (8), visual hallucination (1), insomnia (1), vertigo (1) or lack of concentration (1)), gastrointestinal symptoms (nausea and vomiting (4), diffuse abdominal pain (1), right upper quadrant abdominal pain (1), jaundice (1)) and one anaphylactic reaction. Eighteen courses (7.1%) were discontinued due to AEs that were at least possibly related to voriconazole treatment (skin eruptions (7), increased liver function parameters (7), nausea and vomiting (2), anaphylaxis (1), neurotoxicity (1)).

Increases in hepatic function parameters during therapy were frequent. However, while mean aspartate aminotransferase (AST), alkaline phosphatase (ALP) and serum bilirubin values were slightly elevated at end of treatment ($p<0.01$, Wilcoxon signed rank test), mean alanine aminotransferase (ALT) and serum creatinine values were not different from baseline (Figure 1). We observed moderate correlations between maximum daily dose (mg/kg) per episode and maximum AST or alkaline phosphatase values (Spearman's rank correlation coefficient $r$, 0.231–0.326, $p \leq 0.01$), but there were no consistent relationships between voriconazole dose and other laboratory parameters observed during or at the end of treatment.

## Responses to treatment

Responses to treatment with voriconazole are listed in Table 4. 187/215 (87.0%) courses of primary/secondary prophylaxis or empiric therapy were completed with success. Reasons for treatment failure included possible pulmonary mould breakthrough infection in seven cases, proven pulmonary mould breakthrough infection in one case and candidemia in another case. Three patients of the prophylaxis cohort died from their underlying conditions and in 13 cases AEs, that were at least possibly related to voriconazole, caused discontinuation. Empiric therapy failed overall three times (deterioration of (1) and death by (1) pneumonia and sepsis of unknown origin, possible disseminated candidiasis (1)).

Among the 25 courses with probable and proven IFDs, complete or partial responses were observed in seven courses and stable disease in ten courses. Eight patients failed therapy with voriconazole (death due to invasive pulmonary aspergillosis in one and progressive disease in seven cases (pulmonary aspergillosis (3), candidemia (2), pulmonary trichosporonosis (1), disseminated aspergillosis (1)). Among the twelve courses administered for possible IFDs, six had a complete, and three a partial response; stable disease was observed in one course, and in two courses, treatment failed (progressing lung infiltrates (1), progression of infiltrates in liver and spleen and new pulmonary infiltrates (1)).

Altogether, 203 of 252 treatment courses (80.6 %) were completed with success, and 49 were considered treatment failures. Overall survival was 97.6% at the end of treatment and 92.1% three months post end of treatment, respectively. No correlations between maximum dose/episode and treatment response were found in the overall study population and in subgroup analyses.

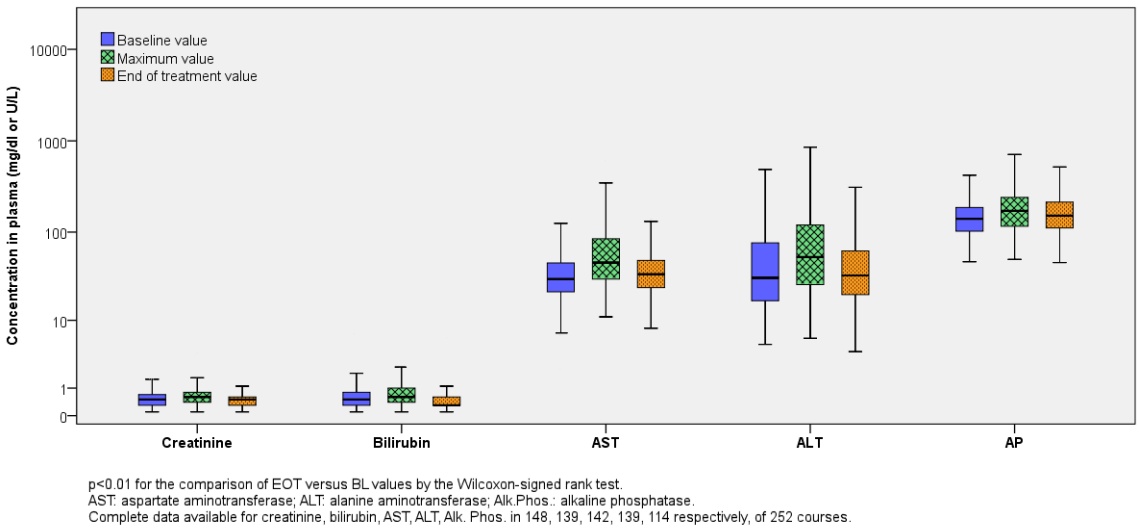


**Figure 1: Dynamics of laboratory values during treatment with voriconazole. Depicted are hepatic and renal function parameters (median, minimum, maximum and inter-quartile range) of the entire cohort at baseline (BL), at end of treatment (EOT) and the maximum values observed during therapy.**

**Table 4: Responses to treatment in 252 courses of voriconazole**

| Response | Primary prophylaxis (n=127) | Secondary prophylaxis (n=79) | Empirical therapy (n=9) | Possible IFD (n=12) | Prob./prov. IFD (n=25) | All (n=252) |
|---|---|---|---|---|---|---|
| Complete | NA | NA | NA | 6 | 6 | NA |
| Partial | NA | NA | NA | 3 | 1 | NA |
| Stable | NA | NA | NA | 1 | 10 | NA |
| Failure | 15 | 10 | 3 | 2 | 8 | 49* |
| Success | 112 | 69 | 6 | NA | NA | 203 |

IFD: invasive fungal disease

* pl. note that stable disease in possible/probable/proven IFDs was counted as failure

# Discussion

The results of this large retrospective single-center analysis attest to the safety and efficacy of voriconazole in profoundly immunocompromised children and adolescents receiving the compound for prophylaxis or empirical and targeted treatment of life-threatening IFDs. The rate of treatment discontinuations due to AEs that were considered to be at least possibly related to voriconazole treatment was 7.1%. This rate is within the range of 5 to 19% reported by other pediatric series with sufficient data [18], [19], [20], [21]. No unexpected toxicities were observed, and, similar to previous reports, increases in hepatic transaminases were most commonly observed, followed by skin eruptions, neurological events and digestive tract AEs [18], [19], [21], [22]. The exact incidence of AEs not leading to treatment interuptions, however, needs to be interpreted with caution as they are most likely underestimated due to the retrospective nature of analysis.

While abnormal liver function tests can be estimated to be not uncommon in severely immuncompromised patients with relevant comorbidities and a variety of concomitant therapies, the reported frequency of elevated liver function tests in pediatric patients receiving voriconazole varies between 8 and 57% [18], [21], [23], [24], [25]. In our study, abnormal hepatic function parameters occurred in up to 54% of the patients, but were mostly mild to moderate and did not show consistent trends during voriconazole therapy. Moreover, no consistent relationships were found between the daily dose and the occurrence of hepatic AEs.

The clinical and biochemical hepatotoxicity of voriconazole was examined by Amigues et al. in a large retrospective study in adult and pediatric HSCT recipients [26]. Sixty-eight of 200 patients (34%) developed hepatotoxicity while on voriconazole, and thirty-five patients (51%) with hepatotoxicity required discontinuation of therapy. There were no cases of liver failure or death attributed to voriconazole, and, with the exception of total bilirubin, the hepatic dysfunction was generally mild and reversible. In multiple logistic regression analysis, acute GVHD grades 2–4 (P=.002) was the only risk factor significantly associated with hepatotoxicity. Whereas another study did not find that patients with hepatotoxicity had received higher than the standard 4 mg/kg doses [27], other investigators found higher total daily doses duration of voriconazole treatment to be associated with hepatotoxic outcomes in adults [28]. A large longitudinal logistic regression analysis on the basis of 2,925 random plasma

samples obtained from 1,053 patients showed a weak, but significant association between 7-day mean plasma concentrations of voriconazole and abnormal levels of AST, ALP and bilirubin, but not ALT [29]. Further studies found a correlation between voriconazole trough levels and ALP and AST, but not for bilirubin, creatinine and ALT [30] or not for ALP or GGT [31]. In children and adolescents receiving voriconazole, no consistent correlation between dose or exposure and hepatic AEs has been established thus far [13], [23], [32].

Phototoxic skin reactions have been reported to occur in a frequency of up to 30% in immunocompromised pediatric patients receiving voriconazole as antifungal prophylaxis [33]. A possible association between long-term use of voriconazole, immuno-suppression and chronic phototoxicity with aggressive squamous cell carcinoma has been reported in adult and pediatric patients [34] and it is now established that voriconazole is an independent risk factor for the development of cutaneous malignancy in lung transplant recipients. The mechanism of voriconazole induced skin cancer is still unknown [35]. As a consequence, the risk-benefit ratio for continued treatment in immunocompromised children and adolescents who develop phototoxicity while receiving voriconazole needs to be extremely carefully evaluated.

Visual disturbance (altered or enhanced perception of light, blurred vision) have been reported in approximately 23% of adult patients receiving voriconazole within a clinical trial [3], [6]. In our analysis, photophobia was infrequent and recorded in only 3.2% of 252 treatment courses. This low frequency may be due both to the inability of younger pediatric patients to perceive and report these symptoms and to the retrospective study design. While one pediatric study reported a rate of visual disturbances in 13% of the enrolled patients [36], the observed rates in other studies were in the range of 2 to 5% [18], [24], [37], [38]. Similarly to what has been reported by others, the visual adverse events observed in the patients included in our analysis were transient and reversible. This is consistent with results obtained experimentally in monkeys, which suggest that the function of the retinal ON-bipolar cells is selectively and reversibly affected in voriconazole treated humans who complain of visual disturbances [39].

Neurological AEs associated with voriconazole include hallucinations, particularly visual hallucinations. The rate of hallucinations in voriconazole treated adults has been reported as high as 17% in prospective studies [40], [41], and a relationship between high voriconazole exposure and neurological AEs has been described in adults [31], although this has not been a consistent finding [28]. In pediatric series with adequate data, few or no cases of hallucinations have been reported [21], [25].

Although the assessment of efficacy of voriconazole treatment is curtailed in our analysis by its retrospective nature, different comorbidities and different indications, reporting outcomes is relevant in the context of patient safety. Considering failure rates of 4,4% and 32% in the prophylactic and therapeutic setting, respectively, these outcomes compare favorably with the limited data reported for paediatric patients: In larger cohort studies of children and adolescents with allogeneic HSCT or undergoing treatment for leukemia receiving voriconazole prophylaxis, the failure rates were between 3 and 6% [21], [24], [42], [43], and among 58 immunocompromised children with IFDs receiving voriconazole treatment, 25 (43%) failed therapy [18].

## Conclusions

The results of our analysis and the data discussed indicate that the use of voriconazole in children and adolescents is generally safe and effective in prevention and treatment of IFDs. Nevertheless, while on therapy, patients receiving voriconazole should be carefully monitored for hepatic toxicity, phototoxic reactions, hallucinations, and, based on its association with QT interval prolongation, potentially proarrhythmic conditions. Clinical management should include laboratory evaluation of hepatic function at the initiation of treatment and at least weekly for the first month of treatment and monthly thereafter if there are no changes in the liver function tests. If phototoxic reactions occur, the patient should be referred to a dermatologist. In case of markedly elevated liver function tests or occurrence of phototoxicity, voriconazole discontinuation should be considered unless evaluation of the risk-benefit of the treatment for the patient justifies continued use under systematic and regular further observation [9]. Of note, while therapeutic drug monitoring (TDM) is not recommended by both FDA and EMA [9], [10], international pediatric guidelines suggest TDM to guide voriconazole treatment (dosing target: trough concentrations of 1.0 to 5.0 mg/L) on the basis of the compound's high variability in exposure and demonstrated correlations between exposure and efficacy and adverse events, respectively [44].

## Notes

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This study was supported by internal funding.

### Competing interests

AHG has received grants from Gilead and Merck, Sharp & Dohme; is a consultant to Astellas, Gilead, Merck, Sharp & Dohme and Schering-Plough, and served at the speakers' bureau of Astellas, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon. The other authors declare that they have no competing interests.

## Previous publication/presentation

Part of the data set (101 courses in 74 patients) have been published previously in a manuscript exploring pharmacokinetic variability of voriconazole and dose-concentration-effect relationships of the compound [13]. The results of this analysis were presented in part at the 5th Congress "Trends in Medical Mycology" (TIMM), Valencia, Spain, 2011.

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