Early reports

Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis

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Summary

Background Toxic epidermal necrolysis (TEN) is associated with a 30% death rate. Tumour necrosis factor α (TNF-α) has been implicated in the pathogenesis of TEN. Thalidomide is a potent inhibitor of TNF-α action. We did a double-blind, randomised, placebo-controlled study of thalidomide in TEN.

Methods The patients received a 5-day course of thalidomide 400 mg daily or placebo. The main endpoint was the progression of skin detachment after day 7. Secondary endpoints were the severity of the disease, evaluated with the simplified acute physiology score (SAPS), and the mortality. TNF-α and interleukin 6 were measured.

Findings The study was stopped because there was excess mortality in the thalidomide group—ten of 12 patients died compared with three of ten in the placebo group (Fisher's exact test with Katz's approximation, relative risk=2·78, p=0·03). After adjustment for SAPS, mortality remained significantly higher in the thalidomide group than in the placebo group (exact logistic regression mid-p=0·007; 95% CI for odds ratio 2·7 to infinity). Plasma TNF-α concentration was higher in the thalidomide group than the placebo group on day 2, though the difference was not significant (Wilcoxon rank-sum test p=0·07).

Interpretation Even though few patients were included, our data suggest that thalidomide is detrimental in TEN, possibly because of a paradoxical enhancement of TNF-α production.

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Introduction

Toxic epidermal necrolysis (TEN) is a rare, acute, and life-threatening condition. The incidence is one case per million inhabitants per year.[1] Apoptosis of cells causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms. Cases with the most extensive skin detachment are associated with the poorer prognosis, and a 30–40% death rate. Milder forms are known as Stevens-Johnson syndrome (SJS) or SJS/TEN overlap.[2] TEN is usually drug-related.[3]

At present there is no specific treatment for TEN. Some retrospective studies claimed a benefit of corticosteroids in milder forms,[4] whereas several showed no benefit or even increased morbidity and mortality.[5–7] Plasmapheresis, cyclosporin, cyclophosphamide, and N-acetylcysteine have been used in isolated cases and short uncontrolled series,[8–11] allowing no conclusion on the efficacy. Nevertheless, because the extent of final epidermal detachment is the main prognostic factor,[12] therapies with the potential to stop the process of epithelial necrosis would be valuable during the initial phase of the disease.

Apoptosis is the mechanism of keratinocyte death in TEN, and tumour necrosis factor α (TNF-α) is the likely cause for this and for constitutional symptoms during TEN.[10,13] Thus, TNF-α production is believed to be an early pathogenetic event in TEN.

Thalidomide is a potent inhibitor of TNF-α in vitro and in vivo,[14,15] and appeared beneficial in several acute disorders thought to involve TNF-α.[16,17] We undertook a randomised placebo-controlled study of thalidomide in patients with TEN with the aim of testing the efficacy and safety of thalidomide in stopping the necrolysis process and reducing systemic symptoms during the initial phase of extension in TEN.

Methods

Patients

Patients were enrolled from nine centres representing recruitment of about half the cases of TEN in France. Patients over 18 years old were eligible if they had detachment of epidermis of more than 10% of body surface area,[2] if the disease was still in the initial phase of extension and so had evolved for less than 4 days after the first mucocutaneous symptoms, and if they were expected to survive longer than 48 h. Diagnosis of TEN had to be confirmed with photographs and skin biopsy samples showing full-thickness detachment of epidermis, excluding staphylococcal scalded-skin syndrome. Patients were not eligible if their skin detachment was already above 90% of the body surface area, if skin detachment had not progressed during the previous 48 h, and if they had received therapies that have been claimed to influence TEN evolution (systemic corticosteroids, plasmapheresis, cyclosporin,

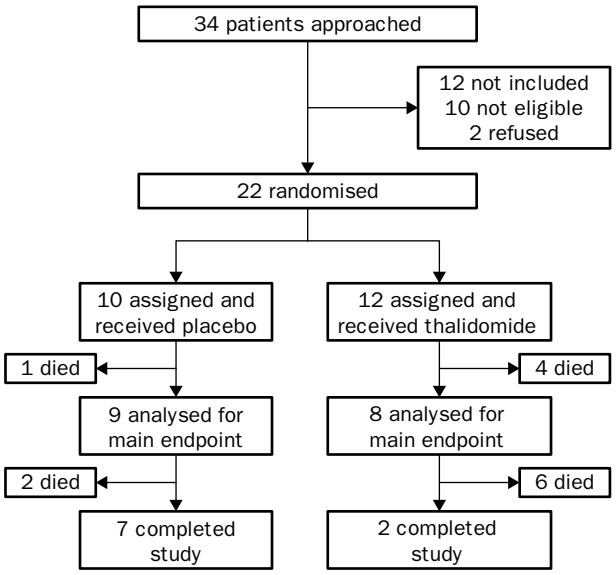

Figure 1: **Trial profile**

cyclophosphamide) or other experimental drugs targeted at TNF-α (such as oxipentifylline or monoclonal antibodies to TNF-α). Women of child-bearing age had to have a negative serum pregnancy test before inclusion. HIV-1 infection was not an exclusion criterion.

Eligible patients were included immediately after admission (day 0). Each patient or the closest relative gave written informed consent for the trial, which had been approved by the ethics committee of Henri-Mondor Hospital according to French law.

Methods

The patients were randomly assigned a 5-day course of thalidomide 400 mg daily or placebo (provided by Laboratoires Laphal, Paris, France). The thalidomide dose was chosen by analogy[16] to that used in the treatment of graft-versus-host disease. The drug was given twice daily as two 100 mg thalidomide capsules or two placebo capsules, orally when possibly or by nasogastric feeding tube otherwise. The placebo and the thalidomide capsules were identical in appearance, and the investigators and patients did not know which capsules were given. The randomisation was done in blocks of six patients stratified according to two categories of study centres—dermatological centres or burns and intensive-care units. Two lists (one for each category of centres) were generated from tables of random numbers. These numbers were assigned to the capsule boxes. Local investigators telephoned a private randomisation service and were given an identification number that matched numbers on capsule boxes distributed in the centres. This schedule was prepared by Laboratoires Laphal; the investigators were unaware of the allocation. A set of sealed envelopes containing the code were supplied to each centre. In an emergency, the code could be broken and the investigator was required to write, sign, and date an explanation. During the study, the code was held by the Clinical Research Department of Laboratoires Laphal. Patients received standard supportive medical therapy (fluids, vasopressors, antibiotics, haemodynamic monitoring, as needed), and the putative culprit drugs were withdrawn.

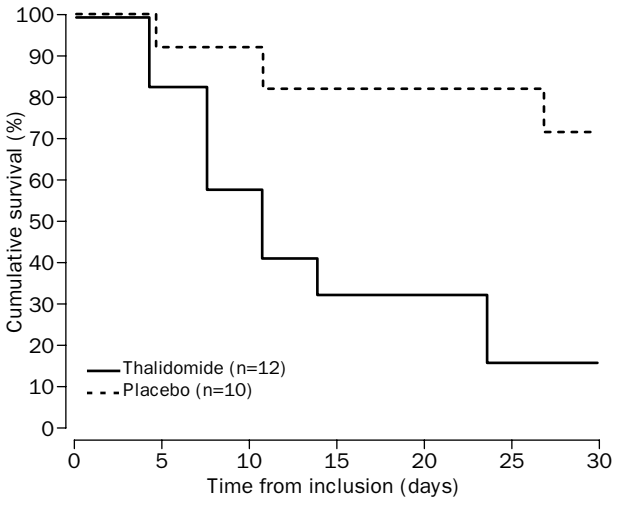

Figure 2: **Overall survival of thalidomide-treated patients compared with those receiving placebo**

On days 0, 5, and 7 the extent of epidermal detachment (erosion, blisters, and areas with positive Nikolsky sign) was measured and expressed as the percentage of body surface area according to classic burns tables.[18]

The main end point of the study was the progression of skin detachment after day 7, assessed as the difference of percentage of skin detachment between day 7 and day 0. Day 7 was chosen so that we could detect a potential rebound after the end of treatment. We also examined progression of skin detachment at day 5, which corresponded to the end of the treatment and to the average delay of skin-detachment progression in TEN. Other endpoints were the overall mortality and the severity of disease evaluated with the simplified acute physiology score[19] (SAPS) at days 5 and 7. SAPS is a prognosis score calculated from seven clinical variables (age, heart rate, systolic blood pressure, body temperature, respiratory rate, urinary output per 24 h, Glasgow coma score) and seven biological variables (blood urea, packed-cell volume, white bloodcell count, and plasma concentrations of glucose potassium, sodium, and bicarbonate). The variations of SAPS were expressed as the difference in SAPS at days 5 and 7 versus day 0.

Plasma and blister-fluid samples for the measurement of TNF-α and interleukin 6 by EIA before and during treatment were obtained on days 0 and 2 and frozen at −80°C. Samples for the measurement of plasma thalidomide concentration were obtained on days 2 and 5. Assays for TNF-α, interleukin 6, and thalidomide were done simultaneously at the end of the study.

Statistics

A sample size of 50 patients (25 in each group) was chosen on the basis of the variability in the maximum percentage of skin detachment in previous TEN series from Créteil centre.[12,20] This sample size allowed us to detect a difference in progression of the percentage of skin detachment between placebo and thalidomide groups of 10% at day 7, with the assumption of an SD of 14% with 80% power at p=0·05 with a one-tailed test.

For continuous variables, appropriate two-sample *t*-tests, Wilcoxon non-parametric rank-sum, or signed-rank tests were used. For categorical variables, Fisher's exact test was used. Because of small numbers, mortality was analysed by exact statistics methods (StatXact Turbo, LogXact Turbo, Cytel Software Corporation, Cambridge, MA, USA). Survival was compared by the Kaplan-Meier method and a log-rank test. An exact logistic regression[21] was done to adjust mortality for potential confounding factors. We did all analyses by intention to treat.

Results

Study population and clinical data

22 patients were enrolled in the study (figure 1) from May, 1995, to September, 1996. Of 15 patients at a single centre (Créteil), nine (60%) had died. This unusually high mortality rate alerted the local investigators. The trial coordinator was informed and decided to convene a safety board of three experts. The safety board first looked at the overall data without breaking the code—13 of 22 patients enrolled had died (overall mortality 59%). Because this rate was higher than expected from previous series of TEN and the baseline severity of patients, the data were analysed

	Group	
	Placebo (n=10)	Thalidomide (n=12)
Age (years)	50·5 (23–58)	53 (23–81)
M/F	4/6	6/6
Weight (kg)	72 (46–105)	56·5 (45–104)
Skin detachment (% BSA)*	30·5 (10–85)	43·5 (26–90)
SAPS	10·5 (6–17)	11·5 (6–19)

Data are median (range).
*% of body surface area.

Table 1: **Demographic and severity features at entry**

by group; there were three deaths among ten patients in one treatment group compared with ten deaths among 12 patients in the other. The decision to break the code was then taken, and the high death rate was found to be associated with thalidomide treatment. Mortality was confirmed to be signifcantly higher in the thalidomide group than in the placebo group (Fisher's exact test with Katz's approximation, relative risk 2·78 [95% CI 1·04–7·40]; p=0·03). The safety board thus advised that the trial be stopped.

Survival curves are plotted in figure 2. Median survival time was 10 days and more than 30 days, respectively, in the thalidomide and placebo groups. Demographic and severity features in the placebo and thalidomide groups are shown in table 1. Among the known prognosis indicators in TEN—percentage of skin detachment and SAPS at entry—only SAPS appeared to be a predictive factor for mortality. After adjustment for SAPS by exact logistic regression, mortality remained significantly higher in the thalidomide group than in the placebo group (exact logistic regression mid-p=0·007; 95% CI for odds ratios 2·7 to infinity).

The progression of skin detachment and SAPS did not differ at day 5 or day 7 between the groups (table 2).

Causes of death

According to the investigators, death was attributed to several causes: multiple organ failure (two in placebo group, six in thalidomide group) septic shock (three in placebo group, five in thalidomide group) and acute-respiratory distress syndrome (three in thalidomide group).

Biological data

Serum concentrations of thalidomide in the treated group were 0·619 mg/L (SD 0·322) at day 2 (data on eight patients) and 0·454 mg/L (0·230) at day 5 (data on seven patients).

The plasma and blister-fluid concentrations of TNF-α and interleukin 6 were high in both groups at day 0 and

	Median (range) change in group*		
	Placebo	Thalidomide	p (Wilcoxon test)
Skin detachment			
Day 5 minus day 0†	−5% (−20% to 23%)	−4% (−65% to 74%)	1·00
Day 7 minus day 0‡	−5·7% (−45% to 20%)	4·9% (−81% to 74%)	0·78
SAPS			
Day 5 minus day 0†	−1 (−6 to 4)	−4 (−3 to 7)	0·14
Day 7 minus day 0‡	0 (−9 to 4)	−2 (−4 to 9)	0·89
Mortality	3/10 (30%)	10/12 (83%)	0·03

*Positive values indicate that skin detachment or SAPS increased to day shown; negative values indicate a decrease.
†Data based on nine patients in each group (one patient in placebo group and three in thalidomide group died before day 5).
‡Data based on nine patients in placebo group and eight patients in thalidomide group (one and four patients, respectively, died before day 7).

Table 2: **Responses according to skin detachment, SAPS, and mortality**

	Median (range) in group		
	Placebo group*	Thalidomide group†	p
Plasma TNF-α (ng/L)			
Day 0	34 (16–392)	58 (16–775)	0·62
Day 2	36 (2–432)	93 (38–636)	0·07
Blister fluid TNF-α (ng/L)			
Day 0	183 (16–1288)	323 (95–1285)	0·51
Day 0	104 (0–314)	103 (45–1279)	0·56
Plasma interleukin 6 (ng/L)			
Day 0	206 (30–32 398)	146 (23–24 109)	0·57
Day 2	278 (70–20 087)	883 (57–11 424)	0·76
Blister-fluid interleukin 6 (ng/L)			
Day 0	1732 (79–2843)	1412 (65–19 468)	0·84
Day 2	722 (142–43 971)	7147 (88–37 802)	0·60

*n=8 on day 0; n=7 on day 2 (except for blister-fluid TNF-α).
†n=12 for day 0 plasma values; n=11 for day 0 blister-fluid values; n=9 for day 2 plasma values; n=10 for day 0 blister-fluid values.

Table 3: **Plasma and blister-fluid TNF-α and interleukin 6 concentrations**

day 2 (table 3). At day 2, the plasma TNF-α concentration was higher in the thalidomide group than the placebo group, though the difference was not significant (p=0·07).

Discussion

This study is the first double-blind, randomised, placebo-controlled trial of any therapy in TEN. Thalidomide was not effective in halting the necrolysis process during the initial phase of extension. On the contrary, thalidomide treatment was associated with increased mortality. This difference was not the result of an unexpectedly low rate of death in the placebo group, because the mortality rate in that group was of the same order in previous series.[12,20] The mortality remained significantly higher in thalidomide receipients after adjustment for SAPS. The causes of death (multiple organ failure, septic shock, and acute respiratory distress) are the usual causes of death in most series of TEN.[12,18]

Thalidomide has been used in several disorders in which TNF-α is thought to play a part[14] and has shown evidence of efficacy in several.[16,17,22] Nevertheless, thalidomide was not successful as prophylaxis for chronic graft-versus-host disease—patients receiving thalidomide had a higher rate of this complication, which resulted in a higher mortality rate.[23]

The excess mortality in our study could be explained by three main causes. First, thalidomide therapy might have resulted in increased mortality through some of its known side-effects—central depression of ventilation by sedative effect or increased bacterial translocation by decrease in gastrointestinal motility.[24] We observed no evidence in favour of these mechanisms. Second, anti-TNF-α might have a protective effect during TEN, as has been suggested in septic shock, in which anti-TNF-α agents may result in increased mortality.[25] However, our data suggest that thalidomide did not inhibit TNF-α production. Third, thalidomide might have resulted in paradoxical overproduction of TNF-α, explaining in part the excess mortality. In our study, plasma concentrations of TNF-α tended to increase after treatment with thalidomide in comparison with the placebo group. Jacobson and colleagues[22] observed a similar unexpected increase in the plasma concentrations of TNF-α and soluble TNF-α receptors with thalidomide treatment for oral aphthous ulcers in HIV-1-infected patients. In-vitro findings[26,27] suggest that thalidomide, at concentrations achieved in vivo, could either enhance or suppress the synthesis of TNF-α depending on the type of cells stimulated. Thus,

thalidomide could enhance, in certain circumstances, the production of TNF-α.[28] Although the trial was stopped after inclusion of only a few patients, our findings suggest that thalidomide is detrimental in TEN, possible because of a paradoxical enhancement of TNF-α production.

Contributors

Jean Revuz, Pierre Wolkenstein, Jean-Claude Roujeau, and Jacques Latarjet designed the study. Corinne Duguet and Sylvie Boudeau collected and checked the data. Loïc Vaillant, Michel Maignan, Marie-Hélène Schuhmacher, Brigitte Milpied, Alain Pilorget, and Hélène Bocquet did the investigations. Christian Brun-Buisson participated on the safety board and analysed the data with Pierre Wolkenstein. Pierre Wolkenstein, Jean-Claude Roujeau, Christian Brun-Buisson, and Jean Revuz wrote the paper.

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