Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial

*Louis Bernard, Aurélien Dinh, Idir Ghout, David Simo, Valerie Zeller, Bertrand Issartel, Vincent Le Moing, Nadia Belmatoug, Philippe Lesprit, Jean-Pierre Bru, Audrey Therby, Damien Bouhour, Eric Dénes, Alexa Debard, Catherine Chirouze, Karine Fèvre, Michel Dupon, Philippe Aegerter, Denis Mulleman, on behalf of the Duration of Treatment for Spondylodiscitis (DTS) study group**

Summary

Background **Duration of treatment for patients with vertebral osteomyelitis is mainly based on expert recommendation rather than evidence. We aimed to establish whether 6 weeks of antibiotic treatment is non-inferior to 12 weeks in patients with pyogenic vertebral osteomyelitis.**

Methods **In this open-label, non-inferiority, randomised controlled trial, we enrolled patients aged 18 years or older with microbiologically confirmed pyogenic vertebral osteomyelitis and typical radiological features from 71 medical care centres across France. Patients were randomly assigned to either 6 weeks or 12 weeks of antibiotic treatment (physician's choice in accordance with French guidelines) by a computer-generated randomisation list of permuted blocks, stratified by centre. The primary endpoint was the proportion of patients who were classified as cured at 1 year by a masked independent validation committee, analysed by intention to treat. Non-inferiority would be declared if the proportion of cured patients assigned to 6 weeks of treatment was not less than the proportion of cured patients assigned to 12 weeks of treatment, within statistical variability, by an absolute margin of 10%. This trial is registered with EudraCT, number 2006-000951-18, and Clinical Trials.gov, number NCT00764114.**

Findings **Between Nov 15, 2006, and March 15, 2011, 359 patients were randomly assigned, of whom six in the 6-week group and two in the 12-week group were excluded after randomisation. 176 patients assigned to the 6-week treatment regimen and 175 to the 12-week treatment regimen were analysed by intention to treat. 160 (90·9%) of 176 patients in the 6-week group and 159 (90·9%) of 175 of those in the 12-week group met the criteria for clinical cure. The difference between the groups (0·05%, 95% CI −6·2 to 6·3) showed the non-inferiority of the 6-week regimen when compared with the 12-week regimen. 50 patients in the 6-week group and 51 in the 12-week group had adverse events, the most common being death (14 [8%] in the 6-week group *vs* 12 [7%] in the 12-week group), antibiotic intolerance (12 [7%] *vs* 9 [5%]), cardiorespiratory failure (7 [4%] *vs* 12 [7%]), and neurological complications (7 [4%] *vs* 3 [2%]).**

Interpretation **6 weeks of antibiotic treatment is not inferior to 12 weeks of antibiotic treatment with respect to the proportion of patients with pyogenic vertebral osteomyelitis cured at 1 year, which suggests that the standard antibiotic treatment duration for patients with this disease could be reduced to 6 weeks.**

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*Members listed in appendix

Division of Infectious Diseases, University Hospital Bretonneau, Tours, France (L Bernard MD); **Division of Infectious Diseases, University Hospital Raymond Poincaré, Garches, France** (A Dinh MD); **Clinical Research Unit, University Hospital Ambroise Paré, Boulogne, France** (I Ghout MSc, D Simo CRA); **Referral Centre for Bone and Joint Infections, Hospital Diaconesses Croix Saint-Simon, Paris, France** (V Zeller MD); **Unité Mobile des Référents en Infectiologie, Villeurbanne, France** (B Issartel MD); **Maladies Infectieuses et Tropicales, University Hospital, Montpellier, France** (V Le Moing MD); **Division of Internal Medicine, University Hospital, Beaujon-Clichy, France** (N Belmatoug MD); **Mobile Infectious Diseases Unit, University Hospital, Créteil, France** (P Lesprit MD); **Division of Infectious Diseases, Regional Hospital, Annecy, France** (J-P Bru MD); **Division of Infectious Diseases, General Hospital of Versailles, Le Chesnay, France** (A Therby MD); **Division of Infectious Diseases, General Hospital, Bourg en Bresse, France** (D Bouhour MD); **Division of Infectious Diseases, Limoges University Hospital, Limoges, France** (E Dénes MD); **Division of Infectious Diseases, University Hospital, Toulouse, France** (A Debard MD); **Division of Infectious Diseases University Hospital, Besançon, France** (C Chirouze MD); **Division of Infectious Diseases, Bretonneau University Hospital, Tours, France**

Introduction

Pyogenic vertebral osteomyelitis generally occurs as an acute osteomyelitis infection in patients older than 55 years. The estimated incidence of vertebral osteomyelitis is four–ten per 100 000 inhabitants per year in high-income countries,[1–2] and has risen in recent years, increasing the economic burden of the disease.[3–4] The optimum duration of antibiotic treatment is unknown; however, most guidelines regard about 6–12 weeks of treatment as the standard of care,[3–6] although this recommendation is not evidence based.[7–9] Other experts recommend antibiotic treatment for a minimum of 3 months.[3,10,11] Long-term exposure to antibiotics increases the frequency of adverse events, health-care-related infections, costs, and antibiotic resistance.[11–13] We aimed to compare treatment duration with effective antibiotics for 6 weeks and 12 weeks in patients with microbiologically confirmed pyogenic vertebral osteomyelitis.

Methods

Study design and patients

In this multicentre, open-label, non-inferiority, randomised, controlled trial, we enrolled patients with pyogenic vertebral osteomyelitis from 71 medical care centres (infectious diseases, rheumatology, or internal medicine departments) in France. We included patients aged 18 years or older with microbiologically confirmed pyogenic vertebral osteomyelitis and typical radiological features (with MRI or CT scan). Criteria for microbiological identification of the causative agent were isolation in blood culture or by CT-guided vertebral biopsy (fine-needle aspiration biopsy).[14] Women of childbearing age had to be using effective contraception

(K Fèvre CRA, L Bernard); **Division of Infectious Diseases, Bordeaux University Hospital, Bordeaux, France** (M Dupon MD); **Clinical Research Unit, AP-HP, Ambroise Paré University Hospital, Boulogne, France** (P Aegerter MD); **and Division of Rheumatology, University Hospitals of Tours, Tours, France** (D Mulleman MD)

Correspondence to: Prof Louis Bernard, Division of Infectious Diseases, Bretonneau Hospital, University Hospitals of Tours, 37044 Tours, France
lbernard@univ-tours.fr

and to have a pregnancy test (β-HCG) with a negative result. Exclusion criteria were life expectancy of less than 1 year, pregnancy or breastfeeding, presence of a vertebral implant, recurrence of spondylodiscitis, presence of fungal, brucellar, or mycobacterial infection, or absence of microbiological identification.

We obtained microbiological identification of causative bacteria and radiological features of pyogenic vertebral osteomyelitis from each participant before randomisation. The blood sample or vertebral biopsy specimen was cultured with standard microbiological methods with the calibrated loop technique at local laboratories. A minimum of two bacterial cultures was required from different samples taken during the same biopsy or on different blood cultures, yielding the same pathogen (at least three identical specimens if the pathogen was a skin bacterium, such as a coagulase-negative *Staphylococcus* spp, *Propionibacterium acnes, or Corynebacteria*, *Lactobacillus*, or *Micrococcus* spp).[15] Susceptibility testing for different antibiotics was done by disc diffusion and minimum inhibitory concentration (E-test, bioMérieux, Lyon, France) with breakpoints from the European Committee on Antimicrobial Susceptibility Testing and French microbiological guidelines. Patients were randomly assigned after a definite diagnosis of pyogenic vertebral osteomyelitis was established.

The French National Agency for the Safety of Medicines and Health Products, the French Data Protection Agency, and the ethics committee of Versailles University Hospital approved the study protocol (appendix). The study was done in accordance with the ethical principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Written informed consent for participation in the trial was obtained from all patients.

See Online for appendix

Randomisation and masking

Patients were randomly assigned to either 6 weeks or 12 weeks of antibiotic treatment (encompassing any parenteral and oral periods of treatment). Randomisation was done during the first 3 weeks after initiation of antibiotic treatment. A computer-generated randomisation list of permuted blocks, stratified by centre, was used for allocation of treatment duration by means of a central interactive voice response server. The local investigator (physician) in charge of patients enrolled participants into the trial, and the pharmacy delivered the allocated antibiotic treatment. Participants and those administering the interventions were not masked to group assignment; however, the members of the independent adjudication committee responsible for classifying patients as cured or not cured were masked to treatment allocation.

Procedures

Because of the pragmatic design of the trial, adjustments to the antibiotic regimen were made at the discretion of the treating physician. Drug selection by these physicians had to be in accordance with French guidelines, which advocate the use of a combination of oral fluoroquinolones and rifampicin as a first-line treatment whenever possible (appendix).[16] Intravenous oxacillin (Bristopen, Bristol-Myers Squibb, Rueil-Malmaison, France) or cloxacillin (Orbenine, Astellas Pharma, Levallois-Perret, France) was used as parenteral penicillin M. Oral drugs with low bioavailability and poor bone diffusion such as cefixime, fosfomycin trometamol, or nitrofurantoin were not authorised for treatment of pyogenic vertebral osteomyelitis.

One or two clinical investigators took part at each participating centre. Investigators and the coordinating committee met before and twice during the study to harmonise procedures. Members of the coordinating committee convened every 3 months to discuss any problems or inconsistencies that arose during the trial.

Patients were excluded from the study if they did not have at least one follow-up visit, if they died during the first week of treatment, if they did not provide written consent, or if administrative information was missing. Patients were not eligible for per-protocol analysis if the length of their treatment violated the protocol (ie, shortening or extensions of treatment in excess of 6 days). Follow-up visits took place at 6 weeks and 3, 6, and 12 months after the end of antibiotic treatment. Clinical assessments in relation to symptoms of infection and back pain were done at each visit. Blood samples for measurement of serum C-reactive protein and serum creatinine concentrations and a radiological survey were also obtained at each visit. A case report form was used to obtain data for each patient participating in the trial.

Quality of life was assessed by the EuroQol EQ-5D questionnaire on the day of inclusion and at 6-month and 12-month follow-up visits. This questionnaire is a descriptive system of health-related quality-of-life states consisting of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each of which can have one of three responses: no problems, some or moderate problems, and extreme problems. Additionally, the EQ visual analogue scale (EQ VAS) was obtained. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale on which the endpoints are labelled "best imaginable health state" and "worst imaginable health state".[17,18]

To assess compliance, duration of antibiotic treatment was recorded during follow-up visits. Patients were encouraged to consult the outpatient clinic if symptoms of pyogenic vertebral osteomyelitis recurred during follow-up; if so, the management of the patient was at treating physician's preference.

Major adverse events (death, non-infectious cardiorespiratory failure, antibiotic intolerance, neurological complications, new infection other than vertebral osteomyelitis, digestive tract bleeding, endocarditis, and cancer) were reported spontaneously by the patient and were also recorded by asking the patient a non-leading question at each follow-up visit.

Confirmed cure was defined as a sustained absence of fever, pain, and inflammatory syndrome (C-reactive protein ≤10 mg/L) 12 months after the end of treatment. An independent adjudication committee composed of a rheumatologist, an infectious diseases specialist, and a microbiologist, masked to the duration of treatment and antibiotic administration routes, reviewed the medical records of the remaining patients and classified these cases as successes (cured) or failures (non-responders). The remaining patients were those who had pain or fever or C-reactive protein greater than 10 mg/L at the end of follow-up, a protocol violation of treatment duration, a major adverse event during the year after the planned end of treatment, or received a new systemic antibiotic treatment for any reason, or those who were lost to follow-up or died.

Outcomes

The primary objective was a non-inferiority comparison of the proportion of patients who were classified as cured by an independent validation committee, 1 year after treatment. Secondary endpoints, also assessed for non-inferiority, were presence of fever, back pain (by clinical examination and visual analogue scale), C-reactive protein and serum creatinine concentrations at each visit, compliance with allocated duration of effective antibiotherapy, major adverse events, proportion of patients who were not cured at 6 months, quality of life (according to EQ-5D score), microbial resistance (by comparison with initial antibiogram in cases of microbiological documented failure), and identification of risk factors for failure and death.

Statistical analysis

We postulated that the proportion of responders assigned to antibiotics for 6 weeks would not be inferior to the proportion of cured patients assigned to 12 weeks of treatment, specifying a non-inferiority margin of 10%. We calculated the planned sample size of 200 patients per group by assuming a 1-year cure rate of 85% in those receiving an effective antibiotic treatment regimen irrespective of whether the duration was 6 weeks or 12 weeks, using a one-tailed type-I error of 0·025, 80% statistical power, and assuming a 20% dropout rate.

The primary hypothesis of non-inferiority was tested in the intention-to-treat and per-protocol populations. The intention-to-treat population consisted of patients who underwent randomisation and received at least one dose of antibiotic treatment. The per-protocol population consisted of patients who received treatment and for whom the actual duration of continuous treatment complied with the randomly allocated duration, plus or minus 6 days. We calculated exact 95% CIs of the difference between cure rates (6-week group minus 12-week group). In sensitivity analyses, we compared the two regimens, by the same method, using two broader definitions of failure—we regarded all deaths as failures at 1 year, and any extension of treatment duration longer than 6 days as a failure.

We present summary statistics for continuous variables as mean and SD or median and IQR, and for categorical variables as counts and percentages. For secondary outcomes, we used Fisher's exact test to compare the distributions of categorical variables, whereas non-parametric Mann-Whitney's test was used to compare the distributions of continuous variables.

To identify the predictive factors of failure, we developed a multivariable regression logistic model. We included all factors that were significant in univariate analyses as candidate factors in the initial model: age (≥75 years or <75 years), endocarditis (yes or no), *Staphylococcus aureus* infection (yes or no), positive blood culture (yes or no), treatment with oral fluoroquinolone and rifampicin (yes or no), duration of intravenous antibiotic treatment (<7 days or >7 days), and allocated duration of treatment (6 weeks or 12 weeks). We examined the effect of variable exclusion on the Akaike information criterion (AIC) and we chose the model with the smallest AIC.

We also did post-hoc analyses to assess the non-inferiority of 6-week treatment versus 12-week treatment in subgroups defined according to age, *S aureus* infection, immunodepression or diabetes, fluoroquinolone and rifampicin treatment, endocarditis, neurological signs, presence of abscesses, and post-surgical vertebral osteomyelitis. We did statistical analyses with StatXact

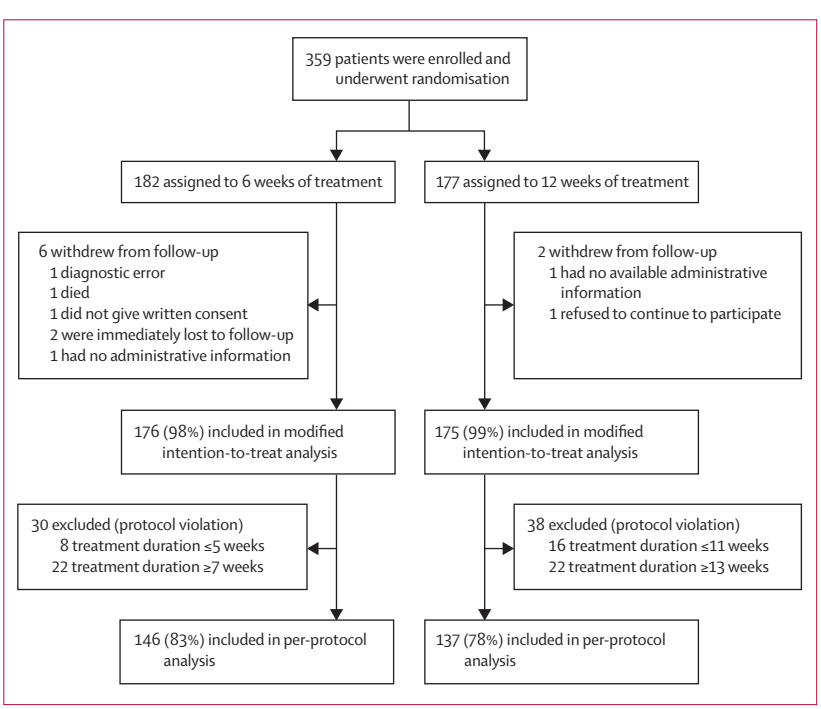

Figure: **Trial profile**
All randomly assigned patients were included in the intention-to-treat analysis except eight patients who were excluded by the independent validation committee. 68 patients whose treatment duration violated the protocol (24 shortening and 44 extensions of 1 week or more than 1 week of treatment) were excluded from the per-protocol analysis.

version 9 for the primary analysis and with R 2.15 software for other analyses.[19–20]

	6-week regimen (n=176)	12-week regimen (n=175)	Total (n=351)
Age, years	62 (16)	60 (17)	61 (17)
Female	61 (35%)	48 (27%)	109 (31%)
Comorbidity			
Immunodepression	5 (3%)	11 (6%)	16 (5%)
Diabetes	36 (20%)	18 (10%)	54 (15%)
Clinical characteristics			
Fever	87 (49%)	95 (54%)	182 (52%)
Back pain	172 (98%)	165 (94%)	337 (96%)
Duration of infection, days	34 (19–58)	34 (18–57)	34 (18–58)
Number of sites of vertebral osteomyelitis			
1	159 (90%)	154 (88%)	313 (89%)
≥2	17 (10%)	21 (12%)	38 (11%)
Type of site of vertebral osteomyelitis			
Cervical level	28 (16%)	24 (14%)	52 (15%)
Thoracic level	46 (26%)	50 (29%)	96 (27%)
Lumbar level	125 (71%)	121 (69%)	246 (70%)
Sacral level	19 (11%)	26 (15%)	45 (13%)
Associated endocarditis*			
Duke definite	23/127 (18%)	28/130 (22%)	51/257 (20%)
Probable	4/127 (3%)	1/130 (1%)	5/257 (2%)
Neurological signs	25 (14%)	32 (18%)	57 (16%)
Radiological biological characteristics			
MRI	157 (89%)	159 (91%)	316 (90%)
CT scan	88 (50%)	80 (46%)	168 (48%)
C-reactive protein concentration			
Absolute concentration, mg/L	118 (103)	126 (108)	122 (105)
Concentration >10 mg/L	157 (89%)	161 (92%)	318 (91%)
Microbiological diagnosis			
Blood culture	119 (68%)	121 (69%)	240 (68%)
CT-vertebral biopsy	67 (38%)	71 (41%)	138 (39%)
Perioperative surgical biopsy	9 (5%)	10 (6%)	19 (5%)
Microbiological identification			
Staphylococcus aureus†	69 (39%)	76 (43%)	145 (41%)
Coagulase-negative *Staphyloccocus*‡	29 (16%)	32 (18%)	61 (17%)
Streptococcus spp	32 (18%)	31 (18%)	63 (18%)
Enterococcus spp	11 (6%)	15 (9%)	26 (7%)
Enterobacterial spp	22 (13%)	16 (9%)	38 (11%)
Anaerobia	7 (4%)	6 (3%)	13 (4%)
Other Gram-negative bacteria	6 (3%)	4 (2%)	10 (3%)
Other *Streptococcus*	4 (2%)	4 (2%)	8 (2%)

Data are mean (SD), number (%), or median (IQR). No significant between-group differences were noted, except that the proportion of patients with diabetes was slightly higher in the 6-week group than in the 12-week group (p=0·024). *227 patients were assessed for endocarditis by echocardiography. †Of the 145 patients with *Staphylococcus aureus,* eight had meticillin-resistant *S aureus* (three in the 6-week group and five in the 12-week group). ‡Of the 61 patients with coagulase-negative staphylococci, 28 had positive CT-vertebral endocarditis biopsies, 15 had positive blood cultures, and 17 had positive CT-vertebral biopsies and positive blood cultures. No significant association between endocarditis and coagulase-negative staphylococci infections was noted (p=0·346); however, post-surgical vertebral spondylodiscitis without implant (PSVS) was a risk factor for osteomyelitis caused by coagulase-negative staphylococci (18 [53%] of 34 PSVS infections were caused by coagulase-negative staphylococci whereas only 43 [14%] of 317 other infections were caused by coagulase-negative staphylococci, p<0·0001).

***Table 1*: Baseline characteristics of the study population**

This trial is registered with EudraCT, number 2006-000951-18, and Clinical Trials.gov, number NCT00764114.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The Clinical Research Unit of Ambroise Paré and the University Hospital of Tours (France) were involved in study design, collection, analysis, and interpretation of data, reviewing the report, and the decision to submit the report for publication. All authors had full access to all the data in the study and had responsibility for the decision to submit for publication.

Results

Between Nov 15, 2006, and March 15, 2011, 359 patients underwent randomisation: 182 patients were allocated to the 6-week antibiotic treatment regimen and 177 to the 12-week antibiotic treatment regimen. Most patients (267 [74%]) were randomly assigned on the day after giving consent (appendix). Eight patients were excluded after randomisation (six from the 6-week group and two from the 12-week group; figure).

Table 1 shows the baseline clinical characteristics of the 351 patients included in the intention-to-treat analysis (176 in the 6-week group and 175 in the 12-week group). More patients had diabetes in the 6-week group than in the 12-week group (table 1). 57 (16%) patients had neurological signs at baseline—37 (11%) of 351 patients had sciatica and 17 (5%) had major neurological motor abnormalities, two (1%) had both sciatica and neurological motor abnormalities, and one (<1%) patient had unknown neurological signs (appendix). 34 (10%) patients had post-surgical (without implant) pyogenic vertebral osteomyelitis (appendix), and 289 (82%) completed 1 year of follow-up (148 [84%] patients in the 6-week group and 141 [81%] patients in the 12-week group).

Of the 351 patients analysed, 68 (19%) had a protocol violation of treatment duration (24 reductions and 44 extensions of at least 1 week of treatment; figure) and were excluded from the per-protocol analysis. The reasons for the protocol violations are listed in the appendix. The remaining 283 patients were assessed in the per-protocol analysis (146 in the 6-week group and 137 in the 12-week group). 62 patients either died, were lost to follow-up, or withdrew from the study. These patients were reviewed and classified as having treatment success or failure (appendix) by the independent validation committee and were included in both the intention-to-treat and per-protocol analyses.

1 year after the end of treatment, 169 (48%) of 351 patients were alive and afebrile with no vertebral pain and with a C-reactive protein concentration of 10 mg/L or less. They were classified as cured without being reviewed by the independent validation committee. Of all other cases (182 patients), the independent validation

committee classified 32 cases as probable failures (16 in the 6-week group and 16 in the 12-week group). The causes of probable failure are detailed in the appendix. Follow-up of patients with back pain did not show any microbiological persistence or relapse of infection due to the same bacteria. Two patients presented with a re-infection of pyogenic vertebral osteomyelitis due to other bacteria. No cases of treatment failure were noted in the 38 patients with enterobacterial infection.

In the intention-to-treat population, for the main analysis, 160 (90·9%) of 176 patients in the 6-week group and 159 (90·8%) of 175 of those in the 12-week group met the criteria for clinical cure (difference 0·05%, 95% CI –6·2 to 6·3). The lower bound of the exact 95% CI of the difference in percentages of cure between the two groups was –6·2%, which met the non-inferiority criterion and was supported by sensitivity analyses (table 2). Non-inferiority was also shown when the eight patients excluded from the primary intention-to-treat analysis were regarded as failures (difference –1·9%, 95% CI –8·6 to 4·7). In the per-protocol population, non-inferiority was also shown; table 2).

Post-hoc subgroup analyses showed that the non-inferiority of the efficacy of a 6-week treatment regimen versus a 12-week treatment regimen was not shown in half of the subgroups (age ≥75 years, infection due to microorganism another than *S aureus*, presence of immunodepression or diabetes mellitus, presence of infective endocarditis, presence of neurological signs, presence of abscesses, prescription of rifampicin and fluoroquinolone, post-surgical osteomyelitis), whereas the superiority of the 12-week treatment regimen was not evidenced in any subgroup (appendix). Overall, all subgroup analyses consistently showed non-inferiority of the 6-week regimen (appendix).

None of the secondary outcome measures, such as fever, pain, C-reactive protein concentration, or serum creatinine concentration (change in these variables over time is presented in the appendix), or failure rate at 6 months, differed significantly between the 6-week and 12-week regimens (table 3). No acquisition of microbiological resistance was reported during follow-up.

With respect to compliance with treatment, eight patients assigned to the 6-week regimen discontinued (one because of a major adverse event, three because of death, and four for unknown or other reasons). 16 patients assigned to the 12-week regimen discontinued (two because of a major adverse event, three because of death, two as a result of loss to follow-up, and five for unknown or other reasons; appendix).

The median duration of antibiotic treatment was 6 weeks (IQR 6–6·6) in the 6-week regimen and 12·1 weeks (12–13) in the 12-week regimen (table 4). The 44 patients for whom actual treatment duration exceeded planned duration by at least 1 week were equally distributed between the two groups (22 [13%] of 176 in the 6-week group *vs* 22 [13%] of 175 in the 12-week group). The most frequently used antibiotics were oral fluoroquinolones or rifampicin or a combination of both in 253 (72%) patients, followed by oral aminopenicillin (98 [28%] patients; table 4). Parenteral meticillin (133 [38%] patients) and aminoglycosides (213 [61%]) were used during the initial intravenous phase of treatment. The distribution of antibiotics did not differ between the two groups for any of the microorganisms assessed (appendix). Median duration of intravenous administration was much the same in both groups (15 days [IQR 7–28] in the 6-week group *vs* 14 days [IQR 6·5–26·5] in the 12-week group). Overall, the median duration of intravenous administration was

	6-week regimen	12-week regimen	Difference in proportion of patients*	95% CI
Intention-to-treat analysis, n	176	175		
Cured	160 (90·9%)	159 (90·9%)	+0·1	–6·2 to 6·3
Cured and alive†	156 (88·6%)	150 (85·7%)	+2·9	–4·2 to 10·1
Cured without further antibiotic treatment‡	142 (80·7%)	141 (80·6%)	+0·1	–8·3 to 8·5
Per-protocol analysis, n	146	137		
Cured	137 (93·8%)	132 (96·4%)	–2·5	–8·2 to 2·9
Cured and alive†	133 (91·1%)	126 (92·0%)	–0·9	–7·7 to 6·0
Cured without further antibiotic treatment‡	NA	NA	NA	NA

Data are number, or number (%) unless otherwise specified. 32 patients (16 in the 6-week group and 16 in the 12-week group) were classified as cases of probable failure of treatment by the independent validation committee. Of 68 protocol violations excluded from the per-protocol population, 18 cases were classified as failure and 50 as cure in the intention-to-treat population. *6-week group minus 12-week group. †Death in cases classified as probable cure by the independent validation committee were classified as failure. ‡Further antibiotic treatment was regarded as a treatment failure. NA=not applicable.

Table 2: **Primary outcome analyses of patients with vertebral osteomyelitis according to duration of antibiotic treatment**

	6-week regimen (n=176)	12-week regimen (n=175)	Total (n=351)	p value
Back pain at 1 year	44/145 (30%)	41/138 (30%)	85/283 (30%)	1
Fever at 1 year (no=0, yes=1)	0	1 (1%)	1 (<1%)	0·48
C-reactive protein concentration at 1 year, mg/L	4·2 (1·9–7·2)	3·2 (1·8–6)	4 (1·8–6·3)	0·22
Adverse events	51 (29%)	50 (29%)	101 (29%)	1
Death	14 (8%)	12 (7%)	26 (7%)	0·85
Cardiorespiratory failure	7 (4%)	12 (7%)	19 (5%)	0·33
Digestive tract bleeding	4 (2%)	2 (1%)	6 (2%)	0·68
Clostridium difficile infection	2 (1%)	2 (1%)	4 (2%)	1
Antibiotic intolerance	12 (7%)	9 (5%)	21 (6%)	0·66
Other infection (not vertebral osteomyelitis)	5 (3%)	7 (4%)	12 (3%)	0·76
Device infection	1 (1%)	2 (1%)	3 (1%)	0·62
Neurological complications	7 (4%)	3 (2%)	10 (3%)	0·34
Endocarditis	3 (2%)	4 (2%)	7 (2%)	0·72

Data are number of patients with at least one event (%) or median (IQR), unless otherwise specified.

Table 3: **Secondary outcomes and adverse events**

14 days (IQR 7–27). The proportion of patients regarded as having treatment failure did not differ significantly between patients who received treatment intravenously for less than 1 week (12 [13%] of 93) and those who received treatment for more than 1 week (20 [7%] of 258; p=0·204). 87 (49%) patients in the 6-week group and 95 (54%) patients in the 12-week group received intravenous treatment for less than 14 days.

During follow-up, 157 adverse events were recorded in 101 patients (50 patients in the 6-week group and 51 in the 12-week group). The major adverse events were death, non-infectious cardiorespiratory failure, antibiotic intolerance (29 events in 21 patients, mainly allergy), neurological complications, a new infection other than vertebral osteomyelitis during follow-up, digestive tract bleeding, endocarditis, and cancer (table 3).

29 reports of intolerance to antibiotic treatment were recorded in 21 (6%) patients of 351 patients (15 in the 6-week group and 14 in the 12-week group): 13 had an allergy (six in the 6-week group *vs* seven in the 12-week group), four had anorexia (one *vs* three), four had blood-cell cytopenia (two *vs* two), one had symptomatic jaundice (in the 12-week group), two had hepatic cytolysis (one *vs* one), and one had confusion (in the 12-week group). The independent validation committee reviewed the 26 deaths (appendix). 13 deaths (ten in the 6-week group and three in the 12-week group) were classified as probable failures, including 11 deaths that occurred during antibiotic treatment: five deaths due to myocardial necrosis (two in the 6-week group *vs* three in the 12-week group), two due to haemorrhage (one *vs* one), two for unknown reasons during follow-up (both in the 12-week group), and one each due to acute respiratory failure (12-week group), severe mitral endocarditis (6-week group), severe urinary tract infection (12-week group), and severe epileptic attack (6-week group).

	6-week regimen (n=176)	12-week regimen (n=175)	Total (n=351)	p value
Treatment duration, weeks	6 (6–6·6)	12·1 (12–13)	9·3 (6–12·1)	..
Oral fluoroquinolone and rifampicin	76 (43%)	79 (45%)	155 (44%)	0·793
Other combinations				..
Rifampicin and aminoglycoside	22 (13%)	25 (14%)	47 (13%)	..
Rifampicin and amoxicillin	3 (2%)	4 (2%)	7 (2%)	..
Fluoroquinolone and aminoglycoside	14 (8%)	11 (6%)	25 (7%)	..
Fluoroquinolone and meticillin	4 (2%)	3 (2%)	7 (2%)	..
Fluoroquinolone and cephalosporin	6 (3%)	6 (3%)	12 (3%)	..
Amoxicillin and aminoglycoside	15 (9%)	17 (10%)	32 (9%)	..
Cephalosporin and aminoglycoside	4 (2%)	3 (2%)	7 (2%)	..
Meticillin and aminoglycoside	2 (1%)	0	2 (1%)	..
Other	30 (17%)	27 (15%)	57 (16%)	..
Intravenous treatment duration, weeks	15 (7·0–28·0)	14 (6·5–26·5)	14 (7·0–27)	0·579

Data are median (IQR) or number (%) unless otherwise specified.

Table 4: **Duration and type of antibiotics used in the study**

The mean EQ-5D index value increased from 0·01 (SD 0·4) at day of inclusion (suggesting poor quality of life) to 0·72 (0·3) at 12-month follow-up (suggesting moderate to good quality of life). Quality-of-life scores did not differ between treatment groups with respect to the five dimensions of the EQ-5D score and the EQ VAS at 6-month and 12-month follow-up (appendix).

The variables significantly associated with treatment failure (n=32) were age (mean age of 67·4 [SD 17·2] years in the 32 patients who were not cured *vs* 60·5 years [16·4] in the 319 patients who were cured; p=0·028) and *S aureus* infection (22 [69%] of 32 *vs* 123 [39%] of 319, respectively; p=0·0012). In multivariable analysis, patients aged 75 years or older, and those with *S aureus* infection, had a higher risk of treatment failure (appendix).

Discussion

In this large, prospective, multicentre, randomised clinical trial, our results showed the non-inferiority of a 6-week treatment regimen versus a 12-week regimen for patients with pyogenic vertebral osteomyelitis meeting strict microbiological criteria and receiving appropriate antibiotic treatment. In our study, non-inferiority of the efficacy of 6-week treatment was not shown in some subgroups (age 75 years or older, or patients with immunodepression or diabetes, endocarditis, or neurological signs), most likely because the size of these subgroups did not provide sufficient statistical power. However, results in all subgroups were consistent with the overall conclusion of non-inferiority of the 6-week group compared with the 12-week group. Independently of the duration of antibiotic treatment, we noted that an age of 75 years or older and *S aureus* infection decreased the chances of treatment success.

The choice of the non-inferiority margin is by definition arbitrary and an issue for debate, because any potential loss of effectiveness can be difficult to defend when the outcome is serious.[21] However, from a practical point of view, 10% is an often-used value for the non-inferiority margin to compare antibiotics.[22] Importantly, the lower limit of the two-sided 95% CI (6·2%) shows that non-inferiority would also have been shown even if a substantially smaller margin had been initially chosen, and provides some additional reassurance with respect to the similar effectiveness of both antibiotic regimens. Further, we need to establish the minimum treatment duration for common infectious diseases in randomised controlled studies.[23]

In the intention-to-treat sensitivity analysis, patients for whom the treatment duration was longer than that allocated by randomisation were regarded as treatment failures, because a cure in these patients might have been due to the extension of their treatment. However, patients for whom a cure was obtained despite a shorter

duration than allocated by randomisation were not regarded as failures, because a cure would have been obtained even if their antibiotic duration had been longer.

One limitation of this trial is its open-label design. Nevertheless, the members of the independent adjudication committee were masked to the duration of antibiotic treatment. Since the choice of antibiotics was left to the treating physician, the use of a placebo for each of the drugs prescribed would have raised insurmountable technical and logistical problems. In our study, 92% of patients were given antibiotics with a high oral bioavailability, such as a fluoroquinolone-rifampicin combination or aminopenicillin. We noted no differences in the distribution of antibiotics used between the two groups, irrespective of the microorganism considered. Furthermore, the proportion of patients cured in our study was as much as that in earlier published data.[5,6,24]

Another limitation of this study is related to the fact that the duration of intravenous use was not standardised. In a retrospective study, McHenry and colleagues[24] postulated that 4–6 weeks of parenteral therapy was the minimum acceptable duration for a favourable outcome in patients with pyogenic vertebral osteomyelitis.[24] In our study, 52% of patients received intravenous treatment for less than 14 days. We showed no significant difference in the proportion of patients with treatment failure between patients given protracted intravenous treatment (>1 week) and those given intravenous treatment for less than 1 week.

This study has several strengths, including its size, multicentre design, recruitment of a high-risk, generalisable population managed with current, guideline-supported drugs and near complete clinical follow-up. In this controlled trial, the conditions and clinical presentations associated with pyogenic vertebral osteomyelitis were similar to those previously reported.[11,25–28] The patients had severe infections—240 (68%) patients had bacteraemia, 11 (3%) of all patients died during the first month, and an additional 15 (4%) died during the year of follow-up. The proportion of patients with pyogenic vertebral osteomyelitis due to coagulase-negative *Staphylococcus* spp (61 [71%] of 351 patients) was higher than that usually reported because we included those with post-surgical vertebral spondylodiscitis.[25]

Our results obtained in a large number of patients in various settings confirm that the microbiological relapse of pyogenic vertebral osteomyelitis is very rare in patients without endocarditis or intracardiac implantable devices (panel).[6,11] Observational cohort studies[29] have shown that patients with meticillin-resistant *S aureus* have poorer outcomes than do those with meticillin-sensitive *S aureus*, whereas other investigators have described exceptional cases of relapse due to meticillin-resistant *S aureus*.[13,30] In our study, we identified no cases of relapse due to meticillin-resistant *S aureus*. Our prospective controlled randomised non-inferiority trial does not target the population of pyogenic vertebral osteomyelitis without microbial identification. The minimum treatment duration in this case needs to be established in randomised trials. The antibiotic treatment duration did not affect quality of life according to EQ 5D assessment. Thus, in patients with pyogenic vertebral osteomyelitis, our results show that 12 weeks of antimicrobial treatment has no clinical advantage over 6 weeks of treatment.

***Panel:* Research in context**

Systematic review

To further assess the effectiveness of antibiotics for 6 weeks and 12 weeks in patients with pyogenic vertebral osteomyelitis, we did an updated meta-analysis of studies comparing these two durations of antibiotic treatment in patients with microbiologically confirmed pyogenic vertebral osteomyelitis. We searched Medline, Embase, Central (the Cochrane Controlled Clinical Trials Register), ClinicalTrials.gov, and proceedings from major infectious diseases scientific sessions for randomised controlled trials comparing 6-week courses with 3-month courses of antibiotic treatment in patients with pyogenic vertebral osteomyelitis. Studies without microbiological identification were excluded. We used the keywords "vertebral osteomyelitis", "spondylodiscitis", "antibiotic duration", and "randomised". We limited the search to studies published between Jan 1, 1980, and May 1, 2014, in English, German, Spanish, or French. We found no Cochrane systematic reviews for vertebral osteomyelitis, epidural abscess, or discitis. Shorter duration of antibiotic treatment is desirable in an era of increasing antibiotic resistance. In one retrospective study,[6] an antibiotic course of 6 weeks was efficacious for treatment of pyogenic vertebral osteomyelitis.

Interpretation

Our results show in an open-label, parallel-group, randomised trial in patients with pyogenic vertebral osteomyelitis that 12 weeks of antimicrobial treatment has no clinical advantage over 6 weeks of treatment, which suggests that 6 weeks of treatment could become the standard treatment. Our results are also valid for older patients (≥75 years) in whom positive blood cultures were more common than in younger patients, and for those with a severe infection. However, the findings should not be extrapolated to patients with other vertebral osteomyelitis due to non-pyogenic microorganisms, meticillin-resistant *Staphylococcus aureus*, or without microbiological identification.

Contributors

LB did the scientific literature search, and LB, IG, and PA were responsible for the study design. AD, DS, VZ, BI, CC, KF, PA, and DM, collected the data, all authors interpreted the data, and AD, IG, BI, VLM, NB, PL, J-PB, AT, DB, ED, AD, CC, PA, and DM analysed the data. LB, AD, IG, and PA created the figures, and all authors were involved in the writing of the report.

Declaration of interests

We declare no competing interests.

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