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Short and long alteplase dwells in dysfunctional hemodialysis catheters

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Abstract

Background: Hemodialysis catheter dysfunction (CD) is the inability to attain adequate blood pump speeds (BPS) and is attributed to thrombus or catheter malposition; alteplase (TPA) is often given in a variety of dwell times to treat CD. The purpose of this study was to determine if TPA dwell time affects short- or long-term catheter patency rates.

Methods: Sixty hemodialysis (HD) patients with CD, as defined by BPS of < 250 mL/min, were randomized to receive either 1- or $>$ 48-hr (to subsequent HD run) TPA dwell. The primary outcomes were catheter patency (BPS of > 250 mL/min) at the subsequent HD run and catheter patency at 2 weeks. The secondary outcome was the time from study entry to the next catheter intervention (including subsequent TPA installation).

Results: After TPA installation, a 78% overall catheter patency rate was observed at the subsequent HD run, falling to 48% patency at 2 weeks. There is no statistically significant difference between the short and long TPA dwell groups for catheter patency at the subsequent HD run (76.9% vs. 79.4%) or at 2 weeks (42.3% vs. 52.9%). Multivariate analysis demonstrates that the use of TPA on two or more previous occasions is a predictor of TPA failure both at the subsequent HD run and at 2 weeks. TPA installation achieves a median catheter function time of only 14 days, after which CD reoccurs.

Conclusion: This study demonstrates that although patency for the next HD run can be achieved with either short or long TPA dwell, neither is reliable in terms of long-term patency. Strategies that employ TPA for CD are temporary and allow a 2-week window during which more definitive therapies for HD access should be sought.

INTRODUCTION

Catheters are the least preferred type of hemodialysis (HD) access compared to arteriovenous fistulas (AVF) and grafts, given their complications of infection, thrombosis, and poor blood flows leading to inadequate dialysis delivery and thus increased patient morbidity and possibly mortality.[1] Nonetheless, they comprise a significant proportion of any dialysis unit's access types. Given the reality of current catheter use and their complications, it is important to examine strategies to prolong catheter longevity and maximize dialysis delivery.

Catheter dysfunction (CD), as defined by the Dialysis Outcome Quality Initiative (DOQI) guidelines, is the inability to attain adequate blood pump speeds (BPS) and is attributed most often to thrombus or catheter malposition.[2] CD leads to inadequate dialysis and subsequent increased morbidity. Occluded catheters, however, are not routinely removed because risks of interrupted therapy and need for repeated venous cannulation resulting in trauma and further patient complications.[3]

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The majority of HD units have established protocols that use either alteplase (TPA) or reteplase in dwell times ranging from 2 to 96 hr as empiric treatment for CD owing to suspected thrombus. There is some evidence[3–11] to support the use of TPA in CD; however, there are no studies that address the optimal dwell time. As such, there are no guidelines regarding dwell time published. In fact, current DOQI guidelines describe the use of urokinase and streptokinase, which were the initial thrombolytic agents tested in HD CD. These agents are no longer widely used owing to the potential risks of anaphylaxis with repeated streptokinase and contamination concerns with urokinase.[3] Given the fact that the majority of North American HD units now use either TPA or reteplase as empiric treatment for CD, we believe it is important to determine the best method of administration. The current study represents the first randomized trial to directly compare the efficacy of two different TPA dwell times for empiric CD. The potential benefit of establishing efficacy of a short dwell time would be early restoration of catheter function and thus better dialysis delivery.

STUDY POPULATION AND METHODS

This study was carried out at St Paul's Hospital, a tertiary-care facility situated in Vancouver, Canada. The study duration was from October 2001 to May 2002 and patients were followed throughout this study period up until June 15, 2002. All patients receiving chronic HD three times a week, 4 hr per session, at the in-center HD unit with either cuffed or noncuffed catheters as primary vascular access were eligible for the trial.

Inclusion criteria were age of > 18 years and dialysis via a temporary or cuffed HD catheter with an episode of CD. The prescribed BPS were the maximal achievable depending on standard venous and arterial pressure limitations of 250 and -250 mmHg, respectively. BPS was defined as the dialysis machine blood flow rate, Qb. All patients were dialyzed on Integra machines (Gambro BCT, Lakewood, CO, USA) using Gambro tubing and Fresenius F80 dialyzers (Fresenius, Bad Homburg, Germany). Patients were excluded if they were hemodynamically unstable and in urgent need of dialysis therapy, had a K^+ of ≥ 6 mmol/L, had a clot documented on a recent catheter dye study, had received TPA within the past two weeks, or if they had been previously enrolled in the study. The study was approved by the Ethics Board of St Paul's Hospital and the University of British Columbia.

Study design

This was a prospective, randomized, nonblinded study. Patients identified as having CD were randomized to receive "short"- or "long"-dwell TPA. CD was defined as per our unit protocol: a persistent BPS of ≤ 250 mL/min with the lines in the normal position, unresponsive to patient repositioning for more than 1 hr of the dialysis run, or any BPS in the reversed position. The nursing staff initially identified CD and the study nephrologist confirmed the diagnosis after review of the dialysis run. In all patients CD was identified within the first hour of the HD session.

Once CD was identified, the HD nursing staff were instructed to follow a standard unit protocol that involved patient repositioning and catheter flushing with saline in an attempt to reestablish blood flow. If these measures were unsuccessful, the attending physician was notified and a preprinted TPA study form was sent to the pharmacy where the patients were block randomized (by blocks of four in a consecutive fashion) to receive either a 1- or a 48- to 72-hr TPA dwell.

TPA (Activase, Roche, East Sussex, UK) was reconstituted and subsequently transferred from bulk multidose vials into sterile prefilled 2-mL syringes at a concentration of 1 mg/mL. In accordance with position statements from published stability data, prefilled syringes were then stored at $-20°C$ in the pharmacy department until needed at which time the syringes were allowed to thaw to room temperature before dispensing.[9] From these prefilled syringes TPA was instilled at a volume determined by the manufacturers specifications of the lumen volume.

Periodic reviews of the pharmacy patient database were undertaken to ensure that every HD patient who received TPA during the study period was accounted for. In accordance with current clinical practice, catheter dye studies were not initially ordered to diagnose CD before TPA instillation.

Outcomes

The primary outcomes were the achievement of BPS of > 250 mL/min throughout the subsequent HD run and the absence of CD for two weeks, the duration of which was determined a priori. The secondary outcome was the time from study entry to the next catheter intervention (either catheter rewiring, replacing, and/or removing or subsequent TPA installation).

The dialysis run sheet was reviewed to obtain the mean BPS recorded before instillation of TPA and the mean BPS of the dialysis run after TPA. To determine whether catheters remained functional after the study TPA was given, patient dialysis records were reviewed at two weeks and again on a monthly basis for the study

duration. Any TPA use subsequent to the 2-week point was documented, as were any catheter interventions as described above. Persistent CD was followed-up with a catheter dye study to determine the etiology of dysfunction (fibrin sheath, thrombosis, malposition) and the results were recorded.

Baseline data included demographic information, etiology of ESRD, and the presence of comorbidities including coronary artery disease, peripheral vascular disease, and diabetes. Current use and dose of antiplatelet drugs, warfarin, and erythropoietin were recorded. Baseline laboratory data obtained from the hospital laboratory included hemoglobin and international normalized ratio. Detailed information was collected in regards to the type of catheter (cuffed or noncuffed), original insertion date, catheter location, site, and number of previous HD catheters. If the patient used TPA in the past three months, the number of times the patient received TPA and the most recent order was recorded.

Estimated sample size

There are no published data that report the success rates of specific TPA dwell times. At present, the published data are based on a combination of dwell times and they report success rates of TPA installation from 70% to 85%. For the purpose of this study we postulated that the short dwell would be more effective than the long dwell because the half-life of TPA is only 4 to 6 min and would inactivate with the longer dwell. Thus we assumed an 85% success with the short dwell and a 70% success rate with the long dwell. The sample size was calculated to detect a difference in success rate of 15% (70% vs. 85%) with a power of 0.80 and a two-tailed alpha of 0.05. Based on these parameters, 120 patients per treatment arm were required.

Statistical analysis

Patient demographic, clinical, and laboratory data were described using mean (± standard deviation) or median (range), depending on the underlying distribution, for continuous variables or frequencies (%) for categorical variables. Continuous variables were compared using the t test or the Wilcoxon rank sum test, where appropriate. Categorical variables were compared using the chi-square test. A p value of less than 0.05 for two-sided univariate tests was considered statistically significant.

Associations between patient and catheter characteristics and success on the following HD run were analyzed using logistic regression modeling. Catheter survival was determined from the time of randomization to the next CD event by using the Kaplan-Meier method. Patients were censored in case of unrelated catheter interventions such as switching to an AVF, planned conversion to peritoneal dialysis (PD), transplantation, or death. Differences between catheter survival times for the short- and long-dwell groups were compared using the log-rank test. The Cox proportional hazards regression model was used to determine predictors of time to next CD.

RESULTS

The trial was conducted over an 8-month duration with a median length of follow-up of 98 days (range, 30–210 days). During the study period, 81 patients had an episode of CD requiring TPA, of which 21 patients were excluded from the study. Reasons for exclusion were nephrologist preference (3), hemodynamically unstable condition (4), documented clot (2), breach of study protocol (4), and unknown (8). Thus, of the 60 patients enrolled into the study, 26 patients were randomized to Group A, 1-hr dwell, and 34 patients to Group B, dwell until next run (> 48 hr); median TPA dwell time in this group was 52 hr.

At six months after enrollment, review of the study protocol with nursing staff was undertaken. At that time there were multiple issues raised from a practical trial execution perspective that led to early termination of the study. Specifically, the 1-hr dwell was impractical, time-consuming, and labor-intensive (30–45 min to confirm CD and order TPA, 45 min to thaw, and the 60-min dwell). After the TPA dwell, patients often only had 60 to 90 min of remaining dialysis. Given the impracticality of the 1-hr dwell design the study enrollment was stopped after only 60 patients and the results of those patients are presented here. The study monitoring board sanctioned this action.

Baseline patient characteristics

The characteristics of the study population are shown in Table 1 and are in keeping with provincial and national demographics. The etiology of end-stage renal disease was: diabetes mellitus (28%), hypertension (22%), glomerulonephritis (13%), and other (37%). The most frequent site of catheter placement was the right internal jugular (75%) followed by the left internal jugular (12%). Very few study patients had femoral and subclavian lines. Forty-nine (82%) of the catheters were tunneled cuffed,

Table 1 Patient baseline characteristics[a]

Variable	1-hr dwell (n = 26)	Next HD dwell (n = 34)
Age (years)	67 ± 17.4	67 ± 14.4
Male sex	18 (69)	19 (60)
Diabetes mellitus status	11 (42)	13 (38)
Peripheral vascular disease	6 (23)	7 (21)
Coronary artery disease	13 (50)	12 (35)
Previous catheters	15 (58)	19 (56)
Two or more previous catheters	4 (15)	9 (26)
Temporary catheter	4 (15)	7 (21)
Current catheter duration (days)[b]	99 (6–1150)	45 (1–1038)
TPA used in past	14 (54)	14 (41)
Two or more TPA used in past	9 (35)	10 (29)
Hemoglobin (g/L)	106 ± 28.8	111 ± 22.9
Erythropoietin weekly dose (U/kg)[b]	144 (0–394)	159 (0–750)
International normalized ratio > 1.5	4 (15)	3 (9)
Aspirin use	9 (35)	6 (18)
Warfarin use	8 (31)	10 (29)

[a]Data are reported as number (%).
[b]Data are reported as median (range).
TPA = alteplase.

all of which were Permcath (Quinton Instruments Co., Seattle, WA, USA). Eleven patients (18%) had temporary catheters (Niagra Vas-cath Inc.). In the trial sample, the median catheter duration at study entry was 56 days and distribution of catheter duration was similar between the two groups.

Catheter patency

Catheter patency, as defined by a BPS > 250 mL/min in the following dialysis run, was attained in 47 (78.3%) of all patients after TPA, irrespective of treatment group (Table 2). The observed difference between the TPA dwell groups of 2.5% was not statistically significant. The 95% confidence interval from −24% to 19% includes a hypothesized difference of 15%; thus we cannot exclude differences that are clinically important. Despite the initial success rate of 78% there was a general decline in TPA efficacy to an overall rate of 48% by 2 weeks (42% in short-dwell vs. 53% in long-dwell patients).

Mean and median BPS obtained before TPA and after TPA were not different between the two groups. The mean BPS following TPA administration improved from 193 ± 48 to 302 ± 57 mL/min (p = 0.0001). The overall change in BPS achieved with TPA was 109 (± 72) mL/min and is not statistically different between the two groups. The median time of catheter function after TPA installation was 14 days (25th-75th percentile, 4–83).

Catheter survival

Figure 1 demonstrates catheter survival as determined from the time of randomization until the next CD event. There is no difference in catheter survival between the short or long dwell groups (with a median of 14 days for the short dwell and 18 days for the long dwell, p = 0.621).

Predictors of CD after TPA dwell

Univariate analysis was performed to determine the relationship between patient and catheter factors and immediate response to TPA. The predictors of immediate TPA failure included the use of TPA on two or more previous occasions before study start (p = 0.052). After adjusting for age, sex, and diabetes status in multivariate analysis, multiple previous use of TPA (odds ratio, 4.38; 95% confidence interval, 1.09–17.54; p = 0.037) remained a significant predictor of immediate TPA failure irrespective of dwell time. Multivariate analysis identified that two or more previous TPA installations (relative risk, 2.303; 95% confidence interval, 1.201–4.416; p = 0.012) was also a significant predictor of CD at 2 weeks.

Table 2 Outcome results

Measure	1-hr dwell (n = 26)	Next HD dwell (n = 34)	P value
BPS (mL/min)			
Before TPA	183 ± 47.6	200 ± 48.1	0.179
After TPA	301 ± 57.4	302 ± 57.8	0.942
Change from before to after	118 ± 73.9	102 ± 71.2	0.403
> 250 mL/min next HD run	20 (76.9%)	27 (79.4%)	0.817
> 250 mL/min at 2 weeks	11 (42.3%)	18 (52.9%)	0.414
CD-free status (days)*	14 (4–83)	18 (4–77)	0.621

[a]Median (25th and 75th percentiles).
HD = hemodialysis; TPA = alteplase; CD = catheter dysfunction.

Patient and catheter follow-up

Of the 31 patients with recurrent CD at two weeks, 21 (68%) underwent a catheter dye study (see Table 3). Of the 10 patients that did not have a dye study, seven had their line exchanged, two transferred to PD, and one died before a dye study was performed. There was no difference between the patients that had a dye study and those that did not in terms of catheter duration or type of catheter. The majority of dye studies demonstrated thrombus (15/21), all of which were found in tunneled-cuffed. Of the 6 nonthrombus dye studies, 2 were normal and 4 showed malposition

Over the 8-month study duration, a total of 38 HD catheters were removed. Catheters were removed primarily for ongoing CD (n = 13, 34%) or transfer to AVF, arteriovenous graft (AVG), or PD because of persistent dysfunction (n = 5, 13%). 10 patients (26%) had functional catheters at the time of transfer to AVF, AVG, PD, or transplant. One patient made a full recovery and subsequently had the catheter removed. There were a total of nine patient deaths throughout this study duration, eight of whom had persistent CD.

DISCUSSION

We report here the first study to randomize HD patients with CD into two groups based on TPA dwell time. The primary aim was to determine whether length of TPA dwell affects the restoration of catheter blood flow. We found no significant differences in success rates of catheter patency between the short or long TPA dwells. Our study, however, was terminated early and we did not

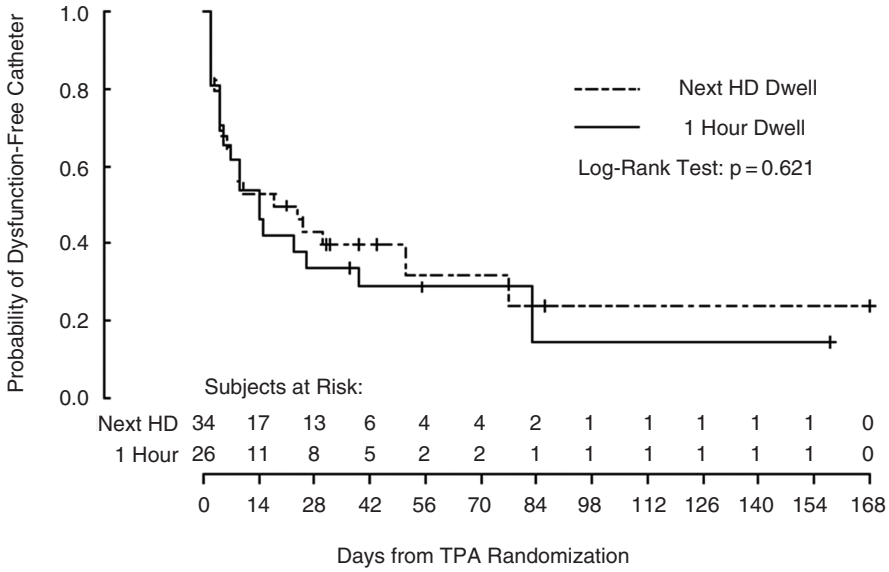

Figure 1 Kaplan-Meier survival curve for time to CD.

Table 3 Dye study results in 21 of 31 patients with CD at 2 weeks

Variable	Thrombus (15 studies)	No thrombus (6 studies)
Tunneled-cuffed catheter	15	4
Temporary catheter	0	2
Mean catheter duration (days)	237	26

CD = catheter dysfunction.

have the sample size to adequately answer this primary question. Despite the early termination of the study, we believe that there are important aspects of this study in terms of methodology and results that warrant description and discussion. Furthermore, these results are based on reasonable patient numbers relative to other TPA HD catheter studies.

Our overall initial catheter patency success rate of 78% is consistent with currently published literature. The decision to set the target BPS after TPA at >250 mL/min resulted in a slightly lower success rate than the studies[5] using a lower target BPS of 200 mL/min. Furthermore, previous studies have used the BPS measured immediately post-TPA dwell to determine the level of success with TPA therapy; we, however, used the common endpoint of next run. This allows a more appropriate comparison, which is clinically important. Because the longer-term success rate obtained with TPA is probably of greater clinical relevance to practitioners than whether the catheter can be used immediately after infusion, we systematically examined catheter function at two weeks after TPA. The study demonstrated that restoration of patency with TPA, although achievable with either regimen, is quite short-lived: catheter patency after dwell decreased dramatically from 78% initially to 48% at two weeks. Overall, we demonstrated a median gain of catheter function of only 14 days after TPA use. Thus we would conclude that although TPA may restore initial catheter function regardless of dwell time regimens, it is ineffective for the long-term management of CD. This is consistent with another publication that described patient follow-up after repeated TPA use: they found the median time until the next intervention is five to seven HD runs (i.e., similar to our median catheter patency of six runs).[10]

The short-dwell method was impractical in our HD unit owing to delays associated with receiving and thawing TPA in addition to the extra workload of stopping the HD session, dwelling the TPA, and restarting dialysis. Despite the impractical aspect associated with the short dwell, however, there are several advantages of this method. The short dwell identifies nonresponders earlier, which then allows for more permanent solutions before the next run. The result would be only one problematic dialysis run, instead of multiple. Furthermore, if the dwell was successful then dialysis is restored sooner to ultimately give the patient better dialysis delivery. Alternatively the advantage of the long dwell is that it does not disrupt the flow in the dialysis unit and add to the nursing workload.

There are several shortcomings of this study. First, we assumed that CD is due to thrombus and installed TPA based on this assumption. This is in keeping with current practice and thus makes the study generalizable. Without radiologic confirmation of actual thrombus, however, some of the TPA failure may have been due to the fact that some of the CD was not due to thrombus formation. Nonetheless, follow-up dye studies confirmed that the majority of CD was due to thrombus, and because the study design reflects current clinical practice, these shortcomings are relative.

The other limitation was that of sample size. Calculations based on the literature would suggest that a sample size of approximately 240 patients was needed, and we stopped recruitment after 60 patients owing to logistical constraints. We were able in a single center to recruit a substantial number of patients and would consider reformatting the study to be a multicenter endeavor in the future.

This study is unique in that it reports the follow-up of persistent CD with catheter dye studies, most of which confirmed the presence of clot either in major vessels or pericatheter. This finding justifies the use of TPA empirically for CD. The lack of a long-lasting effect of TPA given via the dwell and aspirate method in this study may be due to a lack of direct contact with the clot and thus ineffective lysis of large pericatheter thrombi. It may be that an infusion or pulse method for TPA, as described in the DOQI guidelines for urokinase, may be superior. Such an infusion would allow TPA more opportunity to dissolve the clot as it is slowly infused through the entire length of the catheter.[2] Studies comparing the effectiveness of this infusion method of TPA to the traditional dwell method have been started.

CONCLUSIONS

Our study attempted a randomized comparison between two different TPA dwell times to determine the best method of restoring CD. Although this study was underpowered to show a difference between the two methods, it highlighted some important and clinically relevant issues. TPA, using either a short or a long dwell, is effective in improving short-term catheter function; however, it fails to maintain long-term patency with mean

catheter survival of only 14 days. Furthermore, the use of TPA on two or more occasions is a predictor of TPA failure and is an indication to change the catheter rather than attempting recurrent TPA use. Finally, although a short dwell has many advantages such as more rapid restoration of catheter function, it was clinically impractical and led to increased nursing workload and long interruptions in the dialysis treatment. Perhaps improving availability of TPA in the dialysis unit and eliminating the need for thawing the TPA would allow for better delivery of short TPA dwell and make it more feasible.

Regardless of how best to instill TPA, this study confirms the ongoing problems of using catheters for vascular access. Clinicians need to ensure that appropriate long-term vascular accesses are created as quickly as possible. The ability to improve catheter function temporarily should be viewed as just that: a temporary solution to a longer more difficult problem. Nonetheless, efforts to improve current treatment protocols, such as the evaluation of TPA efficacy when administered via infusion, form the basis of our ongoing research.

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REFERENCES

1 Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. *Kidney Int.* 2001; **60**(4):1443–1451.
2 National Kidney Foundation. K/DOQI clinical practice guidelines for vascular access 2000. *Am J Kidney Dis.* 2001; **37**(Suppl 1):S137–S181.
3 Paulsen D, Reisoether AR, Aasen MM, Fauchald P. Use of tissue plasminogen activator for reopening of clotted dialysis catheters. *Nephron.* 1993; **64**(3):468–470.
4 Crowther MA, Stevens L, Ingram A, *et al*. Effectiveness of reconstituted and then frozen t-PA for dysfunctional percutaneous dialysis catheters [abstract]. *Blood.* 2000; **96**(2 Pt 2):4080.
5 Daeihagh P, Jordan J, Chen J, Rocco M. Efficacy of tissue plasminogen activator administration on patency of hemodialysis access catheters. *Am J Kidney Dis.* 2000; **36**(1):75–79.
6 Walton T, Eyrich H. Tissue plasminogen activator use in maintaining patency in hemodialysis access catheters [letter]. *Am J Kidney Dis.* 2001; **37**(2):453A–54.
7 The use of alteplase (t-PA) for the management of thrombotic catheter dysfunction. Guidelines from a consensus conference of the National Association of Vascular Access Networks. *Clinician.* 2000; **18**:2–16.
8 Semba CP, Bakal CW, Calis KA, Grubbs GE, Hunter DW, Matalon TA, Murphy TP, Stump DC, Thomas S, Warner DL. Alteplase as an alternative to urokinase. Advisory Panel on Catheter-Directed Thrombolytic Therapy. *J Vasc Interv Radiol.* 2000; **11**(3):279–287.
9 Little MA, O'Riordan A, Lucy B, Farrel M, Lee M. A prospective study of complications associated with cuffed, tunneled haemodialysis catheters. *Nephrol Dial Transplant.* 2001; **16**:2194–2200.
10 Little MA, Walshe JJ. A longitudinal study of the repeated use of alteplase as therapy for tunneled hemodialysis catheter dysfunction. *Am J Kidney Dis.* 2002; **39**(1):86–91.
11 Clase CM, Crowther MA, Ingram AJ, Cina CS. Thrombolysis for restoration of patency to hemodialysis central venous catheters: A systematic review. *J Thromb Thromb.* 2001; **11**(2):127–136.
12 New applications for thrombolytics: Alteplase in the periphery. *Formulary.* 2001; **36**(Suppl 4):3–15.