

the total time that the immediate and deferred groups spent on zidovudine. They contend that, if the efficacy of zidovudine depended on the duration of its administration, the relatively small exposure to zidovudine before AIDS or ARC appeared in the deferred group would have had little effect. Second, they argue that, if zidovudine were efficacious and its efficacy depended on a particular aspect of disease progression such as a low CD4 count, the CD4 count would have to be below 300/ $\mu$ L since 82% of the patients in the deferred group started zidovudine at CD4 counts of 300 or less. There was no relation between CD4 counts and long-term efficacy of zidovudine.

Despite the change in protocol, analysis of the study was based on intention to treat. Although this is a valid technique, this aspect of study methods in general has been described as "perhaps the chief source of misunderstanding between statisticians and clinicians about the logic of trial design".<sup>7</sup> This method of analysis is appropriate for the Concorde trial and at the very least may have saved numerous arguments about which subgroup should have been included or not. The clinical trial design of Concorde has an ironic aspect in that the exclusion criteria included pregnancy. From the announced outcome of an unpublished study, zidovudine given to the mother during pregnancy reduces the transmission of HIV to the fetus, so a group who might have benefited most from the Concorde study was excluded.

The results showed that, after a median follow-up of 3.3 years, survival was not statistically significantly different between the two groups, with estimated 3-year probabilities of death of 8% in the immediate group and 6% in the deferred group. Progression to AIDS or ARC was likewise similar in the two groups. In a separate analysis of data from the first year, there was a slight advantage to being in the immediate group, with a relative risk (immediate/deferred) of 0.77 at 1 year which lost statistical significance by 18 months. Although there was a consistent difference in CD4 counts, there was no relation between this and a delay in progression of disease.

When a study finds no difference between two groups, one has to consider issues related to the type II or beta error—ie, what is the chance that a difference between the two groups was missed. Of course it is easier to obtain a statistically significant result with larger differences than with smaller ones. Concorde was designed to detect a one-third relative reduction in the rate of progression of disease. From the results, the researchers say that it would have been unlikely for them to have missed a 22% reduction in progression of disease in the immediate group. Since no statistically significant increase in mortality in the immediate group was observed, a relative reduction of more than 9% was judged unlikely.

There is a practical issue in how large a clinical trial can be so as to detect a very small difference between two groups. However, with a disease as devastating as AIDS, a chance of even a 5% reduction in progression may be attractive to an HIV-infected individual. Nevertheless, in taking a chance with treatment, the side-effects of that therapy should be taken into account. Concorde indicates an increased incidence of adverse events in those in the immediate group and the researchers question the impact

on the quality of life of those taking zidovudine. Lenderking et al<sup>8</sup> examined retrospectively a study on zidovudine treatment in symptom-free HIV infection by survival analysis adjusted for the quality of life. They concluded that there was a reduction in quality of life for symptom-free individuals taking 500 mg of zidovudine a day which equalled a short-term gain in disease progression.

The findings of Concorde do not differ from other trials of symptom-free individuals when examined at 1 year. Concorde indicates that the benefit is not lasting, because at 3 years there is little difference between the immediate and the delayed groups. As pointed out previously<sup>9</sup> and referred to in the present study, what is needed is a longer follow-up period to determine what effect the two interventions have subsequently on disease progression and mortality.<sup>2</sup> The question of viral resistance to zidovudine may be related to disease progression. Concorde did not examine viral resistance, but this aspect could usefully be studied during extended follow-up.

Overall, Concorde does not provide compelling evidence that zidovudine is of great use in non-pregnant symptom-free adults with HIV infection.

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## Anticoagulation: how low can one go?

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The high risk of venous thrombosis in patients with advanced cancer presents a therapeutic challenge. Clinicians wish to spare their patients any additional suffering not only from thrombosis but also from intensive treatment or monitoring and from bleeding. Thrombosis prophylaxis with low-dose warfarin, as described in this issue by Levine and colleagues, may provide the answer. Levine et al show that this method is effective and safe. Moreover, oral administration is less troublesome than subcutaneous injections with heparin. Warfarin (and other coumarin derivatives) inhibits the production of all vitamin-K-dependent clotting factors.<sup>1</sup> The effect of a very low dose does not depend on homeopathy: even at an international normalised ratio (INR) of 1.5 clotting factor concentrations are reduced to 50-70% of normal,<sup>2</sup>

and this reduction now proves to be sufficient for substantial protection against thrombosis.

The trend towards less intense anticoagulation has two objectives: (a) to diminish the risk of bleeding, which is closely related to the intensity;<sup>3</sup> and (b) with a fixed-dose, to render frequent monitoring unnecessary. The fixed-dose approach was tried by Poller et al<sup>4</sup> for thrombosis prophylaxis after gynaecological surgery: one group of patients received a fixed dose of warfarin 1 mg daily, and this regimen was compared with controls without anticoagulation and also with anticoagulation in conventional target ranges (INR 2–4). Low-dose warfarin proved effective compared with no treatment (thromboses: 3/32 vs 11/37) but was less effective than full-dose anticoagulation (thromboses: 3/32 vs 1/35). Although the fixed low-dose strategy has clear advantages, it cannot be the first choice because of the great individual variability in doses required to obtain an effect on the clotting system, as confirmed by the broad dose range reported by Levine et al. Poller's study suggests that very-low-dose warfarin is effective, but not as effective as more intense anticoagulation. The same conclusion can be inferred from studies that showed no protective effect of a fixed low-dose warfarin regimen.<sup>5</sup>

The key question now, for all indications, is which intensity of anticoagulation offers the optimum result in terms of balance between effect and side-effect.<sup>6</sup> This answer cannot come from a simple comparison of two target INR levels in a randomised trial: in such a study only two rather arbitrary target intensities are compared, and, more important, the true pharmacological effect is mixed with, or even masked by, imperfect compliance and anticoagulant control. Such factors make interpretation of results difficult, especially when the two target intensities perform equally well.<sup>7</sup> These trials typically use intention-to-treat analyses; the intensity of anticoagulation actually achieved is not taken into account.

Schwartz and Lellouch<sup>8</sup> classified trials as explanatory and pragmatic. In explanatory trials conditions are optimised as in the laboratory to determine the pharmacological effect of a drug. In pragmatic trials conditions are accepted as they are—ie, resembling daily practice—to determine the effect of routine prescribing. These study types differ in design, conduct, size, and analysis: a pragmatic trial will be subjected to an intention-to-treat analysis whereas on-treatment analysis will be used for an explanatory trial.

In oral anticoagulant treatment there is a clear need for explanatory studies. For many indications we now know that coumarin derivatives are effective in preventing thromboembolism—but effectiveness cannot be equated with optimum effect. The preferable on-treatment analysis would require researchers to estimate the risk of untoward events at different achieved intensities. Since INRs vary considerably over time in individual patients, a new method is needed in which "time-spent-at-each-INR" becomes the unit of analysis. Such an approach has recently been developed<sup>9</sup> and is being used in several studies.<sup>10,11</sup> This approach may be pragmatic as well as explanatory, since it can be applied within a randomised trial (as for on-treatment analysis) and also on routine data from anticoagulant clinics.<sup>3,9</sup>

Once we know the optimum achieved intensity of anticoagulation for various indications, subsequent

research should focus at how to achieve these intensities, which remains a major challenge.

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## Microfilaria, tolerance, and T cells

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As shown by Steel and colleagues in this issue, prenatal or perinatal exposure to microfilarial antigens leads to long-term reduction in T-cell responses in vitro but with preserved or enhanced serum antibody concentrations. The effect is specific for antigens restricted to one stage of parasite development, and may explain the absence of certain inflammation-dependent complications such as elephantiasis when such individuals become infected after birth. Various maternal infections can influence the subsequent immunological responsiveness of the offspring.<sup>1</sup> Sometimes trans-placental infection of the fetus is responsible but this does not seem to be the case with microfilaria. Indeed, the immune system of the human fetus can be sensitised to protein antigens of tetanus toxoid injected into the mother.<sup>1,2</sup> In this example, T-cell responses are enhanced, whereas in the report of Steel et al such responses, as assessed by proliferation and cytokine production, are reduced.

Notwithstanding the potentially important implications for pathogenesis, the most interesting aspects of reduced T-cell responses after exposure to microfilarial antigen are speculations about underlying fundamental mechanisms of tolerance induction. Steel et al suggest deletion or paralysis of antigen-specific precursors of functional T-cell clones by exposure to microfilarial antigen in utero. A similar mechanism may play an important part in