Cyclosporins Past, Present, and Future

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IT HAS taken more than a decade of using Sandimmune in daily clinical practice to understand its limitations and identify those properties that are amenable to improvement. First and foremost, the full potential of this impressive immunosuppressant could not be exploited because of the occurrence of side effects. Secondly, variable drug exposure has resulted from poor and unpredictable intestinal absorption. Thirdly, the need for hepatic metabolism before excretion has made bioavailability vary with liver function and has resulted in a large quantity and number of metabolites that have made blood level monitoring complex.

It has been these drawbacks that have motivated the search for new cyclosporins with an improved drug profile. Clearly, only clinical trials can determine with certainty how any new drug performs in humans. Yet laboratory experiments, in which new cyclosporins are compared to those older cyclosporins that have already been tested in humans, have guided the search for improved immunosuppressants. In addition to Sandimmune or cyclosporin A (CyA), cyclosporin G and cyclosporin dihydro D have also been tested in clinical trials. Based on laboratory comparisons to them, the new cyclosporine, SDZ IMM 125, has been selected for clinical development, as a potential successor to Sandimmune.

THERAPEUTIC DOSE RANGE

Today, there are few problems in identifying cyclosporins with good immunosuppressive properties. As a modern alternative to the mixed lymphocyte reaction for general screening purposes, the introduction of a state-of-the-art reporter gene assay has provided an easy and reliable system for quantifying immunosuppressive potency in a human-derived T-lymphocyte cell line. Using this in vitro system to determine the concentration giving half maximal inhibition, the IC_{50}, it is now quite clear that cyclosporin dihydro D is a very weak immunosuppressant, that cyclosporin G is of similar potency to CyA, and that SDZ IMM 125 is marginally more potent than the others.

However, this information is of little value in assessing how cyclosporins will perform in vivo, when absorption, distribution, and metabolism determine therapeutic efficacy, and dosage is frequently limited by side effects. Correspondingly, as depicted in Fig 1, a more appropriate test of potential clinical usefulness is to define the therapeutic dose range that separates the effective dose from the toxic dose. Here, efficacy is inverted and expressed as a percentage of the maximum response, and toxicity is expressed as the factor by which any parameter has changed, relative to the control values.

The therapeutic dose range for CyA in rats is illustrated in Fig 2. Efficacy was assessed in heart and kidney transplantation and graft-vs-host-disease. Toxicity was evaluated from the rise in plasma creatinine, urea or bilirubin, and the fall in plasma magnesium, relative to untreated control animals. A factor of 2 indicates a doubling if the parameters rise or a halving if they fall. What is important is the dose range that separates efficacy, on the left, from toxicity, on the right, and whether this dose range is widened compared to that of CyA.

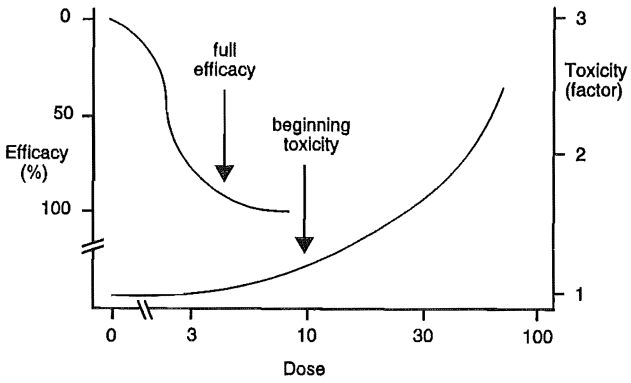

Fig 1. Schematic representation of the therapeutic dose range, with efficacy, inverted and given in percent of maximum response, and toxicity, given as a factor relative to control values, both plotted as a function of log dose.

When the efficacy and toxicity relationship for cyclosporin dihydro D is compared to that for CyA, it becomes obvious that cyclosporine dihydro D, although much less toxic, is also much less potent, giving no indication for an increase in clinical utility. The same comparison of cyclosporin G with CyA shows little difference in the therapeutic dose range between both compounds. However, the therapeutic dose range for SDZ IMM 125, shown in Fig 2, is much wider than that of CyA because therapeutic efficacy is maintained, despite a clear and sustained reduction in toxicity, that persists beyond the doses that are lethal with CyA.

DRUG ABSORPTION

Poor intestinal absorption and the large daily variations in bioavailability can lead to inconveniences with CyA. Recently, the formulation of cyclosporins in vehicles that form microemulsions upon contact with digestive juices

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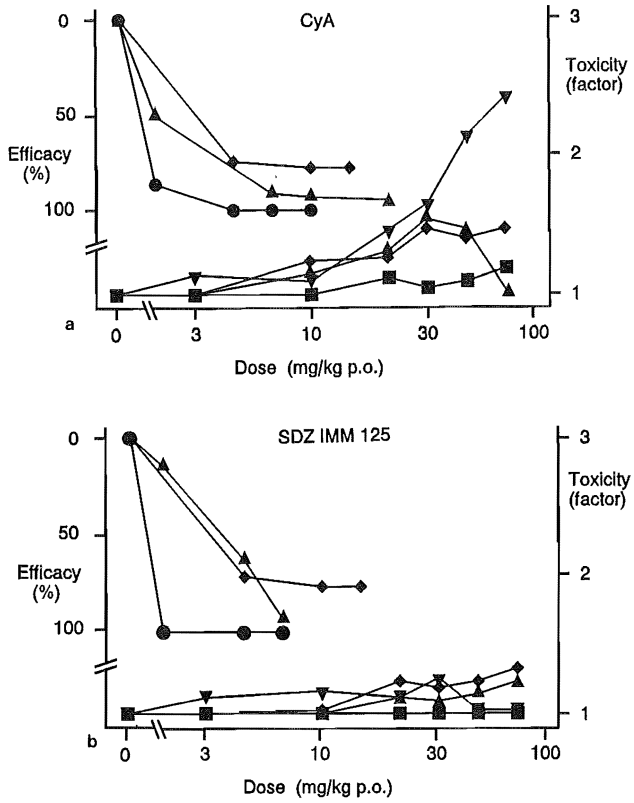

Fig 2. The therapeutic dose range for CyA **(a)** and SDZ IMM 125 **(b)**, as measured after oral dosing in Wistar rats. The efficacy parameters are: ● for kidney transplantation, ▲ for heart transplantation, ◆ for graft-vs-host disease. The toxicity parameters are plasma concentrations of: ▼ for bilirubin, ▲ for urea, ■ for creatinine and ◆ for magnesium.

has greatly improved their intestinal absorption. As shown in Fig 3, a comparison of the blood concentration profile achieved in dogs after oral administration of CyA shows absorption with a microemulsion formulation to be much improved compared to that of the marketed form. However, a comparison of CyA and SDZ IMM 125, applied in the same microemulsion formulation, shows an even more dramatic improvement in bioavailability of SDZ IMM 125 compared to CyA.

DRUG METABOLISM

Drug metabolism is an essential prerequisite for drug excretion with all of the older cyclosporins. This makes bioavailability vary with liver function and results in the presence of not only active parent drug but also many largely inactive, chemically similar, metabolites in blood. As shown in Fig 4, virtually no unmetabolized drug is excreted either in the urine or in the bile of rats after IV administration of CyA or cyclosporin G. In contrast, however, a considerable amount of SDZ IMM 125 can be excreted as unmetabolized parent drug in the bile and a smaller but not insignificant amount can even be excreted unmetabolized in the urine.

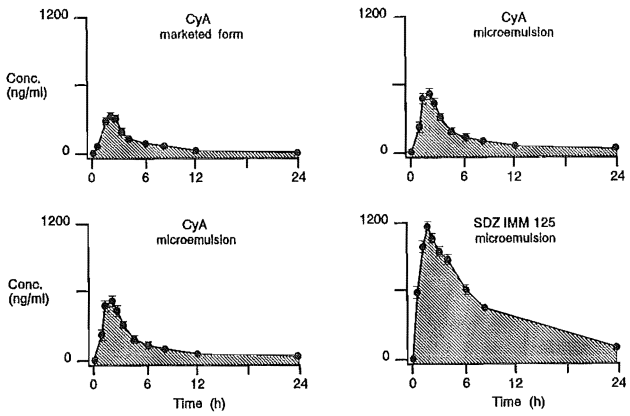

Fig 3. The blood levels of CyA or SDZ IMM 125 measured in dogs after a single oral dose, given as the oil-based marketed form or as a glycofurol-containing preconcentrate that forms a microemulsion.

DRUG DISTRIBUTION

Drug distribution is another important component that determines both drug efficacy and drug toxicity. Cyclosporins show large differences in distribution within the blood stream, as shown in Fig 5, where their concentration in erythrocytes, relative to that in plasma, indicates the degree of targeting to the cellular space, their site of action. For cyclosporin dihydro D and cyclosporin G, less drug is found in the cells than in plasma. For CyA, more drug is found in the cells than in plasma. However, for SDZ IMM 125, much more drug is targeted to the cellular space than to the plasma. Cyclosporins also distribute quite differently into two tissues clearly not involved in immunosuppression as shown in Fig 6. In rats, CyA accumulates in fat and to a lesser extent in muscle in accordance with its high lipophilicity. SDZ IMM 125, in contrast, shows no accumulation in fat and distributes little into muscle.

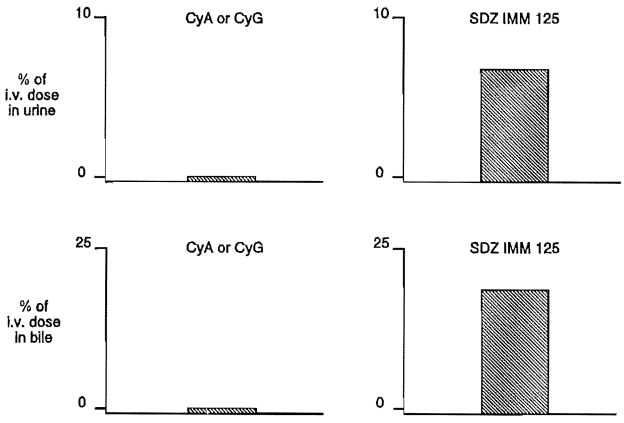

Fig 4. The excretion of unmetabolized parent drug in urine or bile after IV administration of CyA, cyclosporin G, or SDZ IMM 125 to rats.

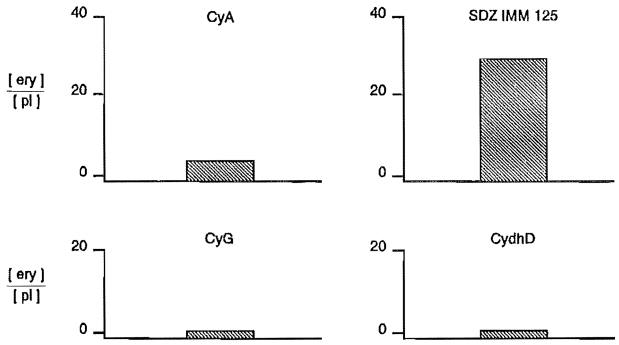

Fig 5. The steady-state red cell to plasma concentration ratio measured in human blood at 37°C after addition of 200 ng/mL of CyA, cyclosporin G, cyclosporin dihydro D, or SDZ IMM 125.

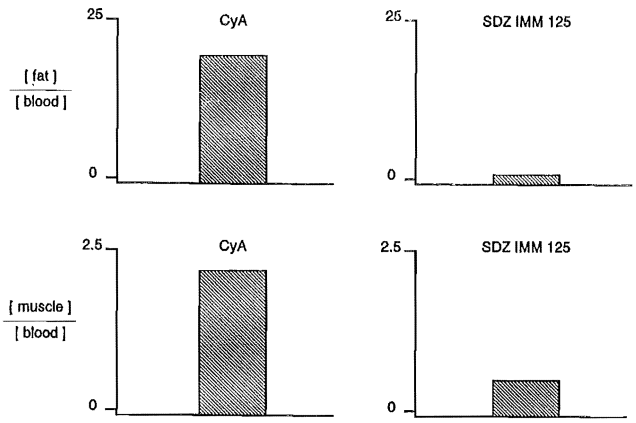

Fig 6. The tissue to blood concentration ratio seen in fat or muscle after application of radiolabelled CyA or SDZ IMM 125 to rats.

SUMMARY AND CONCLUSIONS

Hence, to summarize, it is now easy to identify cyclosporins with high immunosuppressive potency in vitro. What has not been so easy is to establish the relationship between immunosuppression and toxicity in vivo. Now it is possible to identify cyclosporins with a convincing improvement in the therapeutic dose range that promise to be safer clinically. The low intestinal absorption of cyclosporins has been overcome using new galenical formulations that provide high bioavailability. Newer cyclosporins have been identified that need less metabolism before elimination and are better targeted towards the blood cells and away from the bodily tissues and fluids not involved in immunosuppression.

Thus, to conclude and list our expectations for the cyclosporines of the future, including a potential successor to Sandimmune, SDZ IMM 125, we anticipate an immunosuppression that is equal or superior to that of Sandimmune. We want a much wider therapeutic dose range than for Sandimmune. We can guarantee better absorption with less variability than with Sandimmune. We can achieve an excretion of parent drug in both bile and urine. We are confident that there will be less metabolites in peripheral blood. We are encouraged by the lesser distribution into peripheral body tissues. We are optimistic about the improved targeting to the cells of the blood stream. Thus, the cyclosporins are not just drugs of the past but are also drugs that have a great future ahead of them.

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