Transpl Int (1994) 7 [Suppl 1]: S263–S266

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Safety and tolerability of a new oral formulation of cyclosporin A, Sandimmun Neoral, in renal transplant patients

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Abstract The current therapy with Sandimmun has been improved by the development of a new oral formulation of its active ingredient, Cyclosporine A and which is called Sandimmun Neoral. This new galenical formulation is based on the microemulsion technology and offers consistent oral absorption and pharmacokinetic predictability. In two studies of a 12 weeks duration each and including 466 stable renal transplant patients and 86 new renal transplant patients it was shown that Sandimmun Neoral is as well tolerated and as safe as Sandimmun. Stable renal transplant patients currently receiving Sandimmun can safely be switched to Sandimmun Neoral on a 1:1 dose level basis. However, as a result of the more consistent absorption of Sandimmun Neoral, poor absorbers with Sandimmun will become normal absorbers and than will need a considerable dose reduction to reach the same Cyclosporine A exposure. In new renal transplant patients kidney function seems to improve better and faster when Sandimmun Neoral is given as shown by creatinine and creatinine clearance values. In the Sandimmun Neoral group less patients experienced a rejection episode and time free of rejection was longer, this may reflect a better maintenance of immunosuppression. In addition, considerably lower doses (16% on average) are required for Sandimmun Neoral to achieve comparable cyclosporine A blood trough levels and these patients are also sooner stabilized in terms of Cyclosporine a therapy.

Key words Sandimmun
Sandimmun Neoral
Renal transplantation
Immunosuppression

Introduction

Sandoz has improved the current therapy with Sandimmun by developing a new galenical formulation for its active ingredient Cyclosporin A (CsA), which is called Sandimmum Neoral. This new formulation is based on microemulsion technology [1]. Pharmacokinetic studies in healthy volunteers and stable renal transplant patients [2–6] have demonstrated that, when compared with Sandimmun, Sandimmun Neoral has:

- a more consistent absorption independent of food
- less variability in pharmacokinetic parameters
- dose linearity in CsA exposure

A drug providing reliably consistent blood concentrations would greatly facilitate dose individualization in

the management of patients during CsA therapy and would therefore have a beneficial effect on graft survival [7]. Two studies have been performed to investigate its safety and tolerability as well as to target the CsA blood trough levels in a predefined range. These investigations involved stable and new renal transplant patients.

Materials and methods

In a first study 466 stable renal transplant patients were included. For these patients at least 6 months must have passed since their first or second transplant, and Sandimmun had to be part of their immunosuppressive regimen. They had to be stable in terms of graft function, physical and laboratory indices. After a 2-week run-in phase during which all patients received Sandimmun to check baseline stability, patients were randomized in a 4:1 ratio to switch to Sandimmun Neoral on a 1:1 dose level basis or continue Sandimmun for a 12-week period.

Eighty-six new renal transplant patients were randomized at the start of oral therapy, 45 to Sandimmun Neoral and 41 to Sandimmun. The initial dose of study medication was based on the center's local protocol and was then adjusted according to standard rules to achieve a target trough level or for clinical requirements.

Results

Study with stable patients

Although the randomization was unbalanced, the two treatment groups were matched regarding demographics, disease leading to transplantation, time between transplantation and study start and the immunosuppressive therapy prior to study entry. The two treatment groups were compared with respect to safety and tolerability and ease of maintaining CsA blood trough levels within an individually predefined range over the study period.

Tolerability

Adverse events, including also CsA-related side-effects which were elicited or spontaneously reported, were not different in frequency or severity between the groups (68% in the Sandimmun Neoral group versus 62% in the Sandimmun group). In each group nearly 10% of the patients reported a serious adverse event. Very few rejection episodes occurred (only 3 in 466 patients over 12 weeks); all were taking Sandimmun Neoral, so it may be a consequence of the unbalanced randomization. Less than 2% in each group discontinued the study.

Safety

Kidney function was assessed by serum creatinine levels. The values remained stable for the majority of the patients during the study.

In the Sandimmun Neoral group the mean serum creatinine level slightly increased at some time points (weeks 2, 4 and 8 after randomization), perhaps because in some patients the increased exposure was not followed by a dose adjustment. Over the entire study period no significant change in creatinine level occurred in either group. This was also true for other biological parameters, which were conventionally measured, including urea, uric acid, liver enzymes and blood lipids.

Dose adjustments

The dose of study medication was adjusted to keep the CsA blood trough level within the predefined range or for clinical requirements. Dose adjustments fluctuated in both groups. However, when Sandimmun Neoral was given, except for 1 week after the switch, fewer dose adjustments were required (Fig. 1). During the study period 36% of patients in the Sandimmun Neoral group and 43% in the Sandimmun group required a dose adjustment. Fewer patients in the Sandimmun Neoral group required a dose increase (12% versus 20% in Sandimmun group), whereas dose reductions were comparable in both groups (33% versus 31%). This reflects the more consistent absorption when Sandimmun Neoral is given. In the majority of cases the dose adjustment was necessary to keep CsA within the predefined range. In nearly 3% of patients in each group this was due to renal dysfunction. Liver dysfuncton or rejection was never given as a reason.

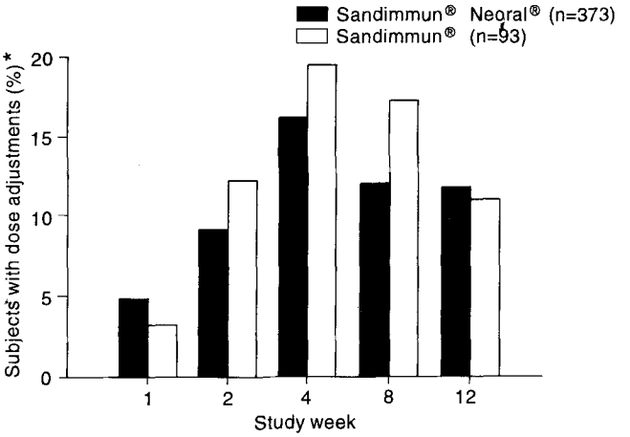

Fig. 1 Dose adjustments in stable renal transplant patients (* dose changes standardised per subject week)

Study with new patients

Regarding rejection episodes, fewer patients in the Neoral group experienced a rejection episode (46% versus 60% in the Sandimmun group). This was still true when multiple rejections were considered. However, 11% in the Neoral group and 20% in the Sandimmun group experienced two or more rejection episodes.

An analysis of the time to first rejection showed that the mean time is longer when the patient received Neoral, 29 days versus 19 days when Sandimmun was given.

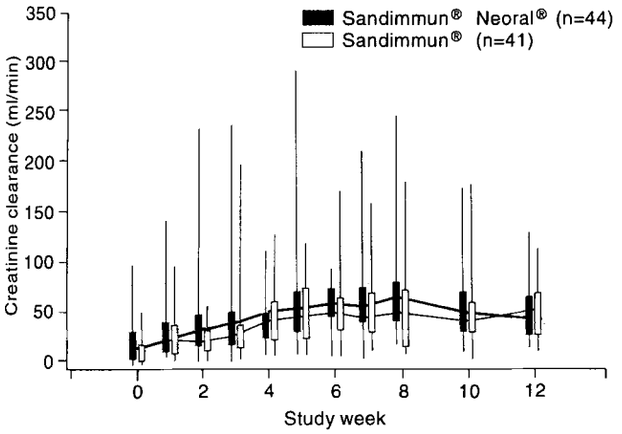

Fig. 2 Creatinine Clearance in new renal transplant patients. Box and whisker plot; the *box* corresponds to the upper and the lower quartiles; the *horizontal line*, the medians; the *extent from the box* to minimum and maximum values

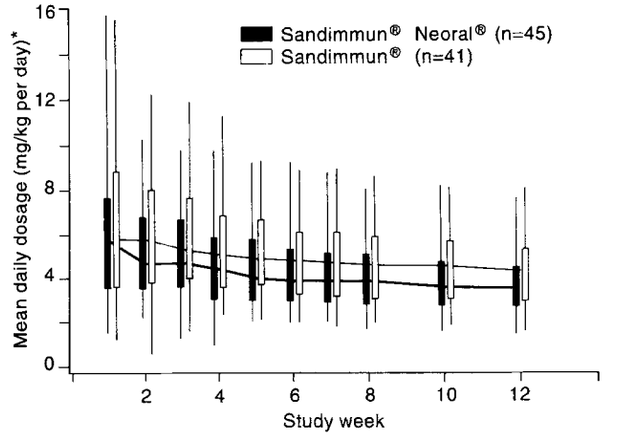

Fig. 3 Mean daily dosage of study medication in new renal transplant patients (* mean daily dosage since previous visit). Box and whisker plot; the *box* corresponds to the upper and the lower quartiles; the *horizontal line*, the medians; the *extent from the box* to minimum and maximum values

Because of the low numbers of patients, the difference between the two treatment groups is not statistically significant, but it is an indication of a better maintenance of immunosuppression when Sandimmun Neoral is given.

Safety

Kidney function was assessed by serum creatinine and creatinine clearance determinations. When patients receive Sandimmun Neoral, the serum creatinine levels decrease faster and of a greater degree. Creatinine clearance also increases faster and more when patients receive Sandimmun Neoral (Fig. 2). This indicates a faster and/or better improvement of renal function when Sandimmun Neoral is given.

Dose adjustments

New renal transplant patients start with high doses of CsA, which decrease until a stable blood trough level is reached. From week 1 onwards this decrease is greater in the Sandimmun Neoral group. At week 12 the mean dose of Sandimmun Neoral was 16% smaller than the Sandimmun dose (3.7 mg/kg daily versus 4.4 mg/kg daily) to achieve comparable CsA blood trough levels (Fig. 3).

The number of dose adjustments decreased substantially over the course of the study (Fig. 4). This number was always lower when Sandimmun Neoral was given, particularly in the second part of the study. This indicates that patients receiving Sandimmun Neoral are sooner stabilized in terms of CsA therapy.

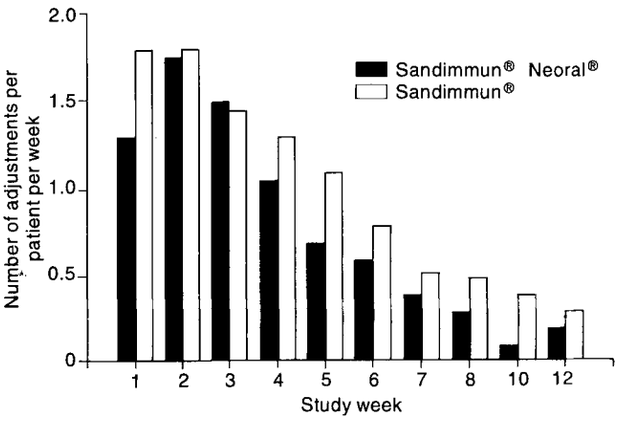

Fig. 4 Dose adjustments in new renal transplant patients

Discussion

Sandimmun Neoral is as well tolerated and as safe as Sandimmun in new and in stable renal transplant patients. Switching stable renal transplant patients currently receiving Sandimmun to Sandimmun Neoral on a 1:1 dose level basis did not lead to an increase in the incidence or severity of side-effects. CsA blood trough levels could more easily be maintained in the predefined range when Sandimmun Neoral was given. The dose can be adjusted in the case of increased exposure. Some patients who develop from poor absorbers to normal absorbers will need a considerable dose reduction.

In new renal transplant patients, kidney function seems to improve better and faster when Sandimmun Neoral is given. In addition, considerably lower doses (16% on average) are required for Sandimmun Neoral to achieve comparable CsA blood trough levels.

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