The Use of Cyclosporine in the Age of Biologics

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Introduction of cyclosporin A has been a major breakthrough in the treatment of psoriasis. Used at doses 2.5–5 mg/kg/day, this drug provides an immediate relief and clears psoriasis in 75–85% of patients. The improvement of patients' quality of life is immense. The very high efficacy is to some extent offset by the side-effects and for that reason cyclosporine has been used as the last resort drug for patients who failed phototherapy and methotrexate monotherapy.

However, what has been acceptable in the past is not necessarily acceptable at present. The situation has especially changed after an introduction of the biological response modifiers, comprising the TNF-α blockers (infliximab, etanercept, adalimumab) and lymphocyte activation inhibitors (efalizumab, alefacept). Many of these novel drugs seem to have a more favourable side-effect profile, making them more interesting candidates for psoriasis treatments than cyclosporine. On the other hand, due to the very high cost of biologic therapy, the drug regulatory agencies wish to limit their use to the narrowly selected high-need patients. According to European recommendations of EMEA, the use of biologics should be limited to the patients who failed or are intolerant to a range of established psoriasis therapies including PUVA, methotrexate and cyclosporine. Leaving aside the economic considerations, I will attempt to assess how sound this recommendation is from a purely clinical point of view.

How safe is it to treat psoriasis with cyclosporine?

This question should probably be re-phrased from "how safe" to "how dangerous". Cyclosporine can exert serious, irreversible side effects. In particular, this drug can produce irreversible kidney damage and increase the incidence of malignant tumors due to its immunosuppressive properties. The likelihood is probably correlated with the cumulative dose. Unfortunately, most data on cyclosporine safety in psoriasis stem from relatively short-termed studies (1–2 years) which would not capture any delayed effects of the drug. The best available evidence of renal side effects of cyclosporine has been gathered from nonrenal transplant recipients. Ojo et al. (1) reported that immunosuppressed transplant recipients have a high incidence of kidney failure attaining values of 6.9% in heart–lung transplants to 18.1% in liver transplants per 5 year period. Chronic renal failure has been associated with a 4.5-fold elevated risk of death. Cyclosporine seems to be more deleterious than tacrolimus (relative risk 1.24).

Very importantly, this study revealed a panel of risk factors for renal failure, each increasing the risk in the range 1.2–1.4. These included increased age, pre-existent hepatitis C infection, hypertension, impaired renal function and diabetes mellitus. This could be important for psoriasis patients. It is likely that transplant recipients are in a poorer general health which would predispose them to a higher incidence of kidney failure. On the other hand, this important study shows a significant risk of renal side effects in patients receiving calcineurin inhibitors. Also evidence from less extensive studies on psoriasis patients suggests a significant risk. In the studies reviewed by Ho (2) between 14% and 71% of treated patients developed renal function impairment which in some instances progressed into histologically discernible cyclosporine nephropathy.

Risk of nephropathy can be justified in patients with life-threatening diseases requiring transplantation. However, psoriasis is not a lethal disease and a single case of cyclosporine-induced nephropathy is one case too many. It is clear that cyclosporine is not the drug of choice for the long-term psoriasis control (3) and its side effect profile seems to be much inferior to that of the available biologics.

What about short-term, intermittent cyclosporine pulses?

Well aware of the risks connected with chronic cyclosporine use, many dermatologists choose to use this drug in the short-term, intermittent mode. Several studies addressed the issue of the efficacy and safety of this mode of treatment (reviewed in

Refs. 2 and 3). Pulses of less than 3 months duration (2.5–5.0 mg/kg/day) appear to be efficacious and not associated with any irreversible side effects. However, the longest intermittent cyclosporine study was of 2 year duration, so we cannot conclude on the long-term safety of this treatment modality. Cyclosporine may not be completely harmless even if used for shorter periods of time. As shown in the above mentioned study of Ojo et al. (1), the risk of kidney failure in transplant recipients was substantial already after 1 year after transplant, ranging from 1.9% (heart–lung) to 8.0 % (liver). Moreover, intermittent cyclosporine treatment is in my opinion a poor modality for the long-term psoriasis control. Unlike phototherapy or methotrexate, the remission periods after cyclosporine are short. The value of pulse cyclosporine treatment is as an add-on to another treatment modality. For example, patients who are well controlled on topical therapy or methotrexate can experience exacerbations, which can excellently be managed by short (1–3 months) courses of cyclosporine.

The role of cyclosporine in the rotational therapy regimes

The principle of rotational therapy is the use of single drugs for a limited period of time, repeating the treatment if necessary. Limited duration of therapy is likely to diminish the long-term side effects due to the cumulative action of a drug. Following this principle it would be conceivable to use cyclosporine safely for the periods of 6–12 months every 2–3 year. However, not all psoriasis therapies are compatible with the subsequent use of cyclosporine. Especially, previous use of PUVA precludes subsequent treatment with cyclosporine due to the risk of squamous cell carcinoma (SCC). This has to be taken seriously, since at least 5% of SCC metastasize. The safe limit of PUVA preceding cyclosporine cannot be established from existing studies. Recent metaanalysis shows that low-dose PUVA (<100 treatments or 1000 J/cm^2) vs high dose (>100 treatments or 2000 J/cm^2) has 8–24 (mean 14) -fold higher risk for SCC (4). Among patients who received high-dose PUVA therapy the risk of SCC does not diminish within a decade after cessation of PUVA (5). Methotrexate has a marginal additive effect on SCC in PUVA patients but UVB does not seem to increase cancer risk. It is therefore unwise to administer cyclosporine to the patients who received multiple courses of PUVA, especially those who have also been treated with methotrexate.

How to use cyclosporine in the age of biologics?

Despite its obvious limitations and safety concerns, cyclosporine is still a valuable drug for psoriasis. However, the pattern of use should, in my opinion, be modified. For the reasons detailed above, the long-term use of this drug should be discouraged. Nobody should die of psoriasis therapy, and it has been shown conclusively that prolonged (> 2 years) use of cyclosporine provides a life hazard. To take this risk could be by some colleagues viewed as unethical, directly contradicting the Hippocratesian commandment "primum non nocere" (first, do no harm). For the long-term control of psoriasis the biologics seem to provide a distinct advantage and should be a preferred mode of therapy. This places cyclosporine as a last resort drug for long-term use in psoriasis.

The preferred use of cyclosporine should be intermittent, short courses. I can think of 4 distinct scenarios in which cyclosporine plays a valuable role:

1. Crisis management in the patients receiving methotrexate or a biologic. Psoriasis may exacerbate as a result of psychological stress, infection, or sun exposure in otherwise well controlled patients. A short-term treatment with cyclosporine provides an instant relief and is probably a safe approach.
2. Cyclosporine course at the initiation of biologic therapy. The onset of action of many biologics, notably etanercept and efalizumab, may be delayed for up to 3 months. Clinical experience shows that cyclosporine can safely be added at the initiation of the biologic therapy providing relief during the "waiting time" with subsequent tapering off after 2–3 months.
3. Cyclosporine as a bridge in the transition period between the biologics. The efficacy of the biologics (with the notable exception of infliximab) does not exceed 50%. It means that at least half of

the patients will not experience the desired effect and would be shifted into another biologic. To avoid exacerbation of psoriasis the patients can be given cyclosporine before termination of the first biologic and continued until the onset of action of the second biologic.

4. Patients in whom psoriasis has a relapsing course. If the patients experiences exacerbations once or twice per year, a short-term treatment could be given, even for the long-term control.

Conclusions

The basis for the recommendation that biologic therapy should only be administrated to the patients who are cyclosporine failures (due to drug intolerance or lack of efficacy) is not clear. Due to safety issues it does not seem ethical to keep all patients on long-term cyclosporine before offering them biologic therapy. A more clinically relevant definition of a patient not eligible for cyclosporine could be formulated as follows:

1. Presence of one or more risk factors (3): current or previous malignancy/pre-malignant conditions (excluding treated basal cell carcinoma), immunodeficiency disorders, abnormal renal function, hepatic dysfunction or hepatitis C infection, hypertension (controlled or uncontrolled), severe infection, diabetes, obesity, age >65 years, drug/alcohol abuse.
2. Previous use of PUVA.
3. Chronic course of psoriasis with short duration of remission.
4. Substantial psoriasis arthritis.
5. Intake of drugs known to interact with cyclosporine (an exhaustive list can be found in Sandimmun Neoral® SPC or in reference 3).

In all these cases short-term cyclosporine treatment can be instituted on the individual basis, but this decision should not influence the decision whether the biologic should be offered.

References

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