

TACHYPHYLAXIS AND REBOUND EFFECTS DO NOT APPEAR TO BE ASSOCIATED WITH USE OF FLUTICASONE PROPIONATE (FP)

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BACKGROUND

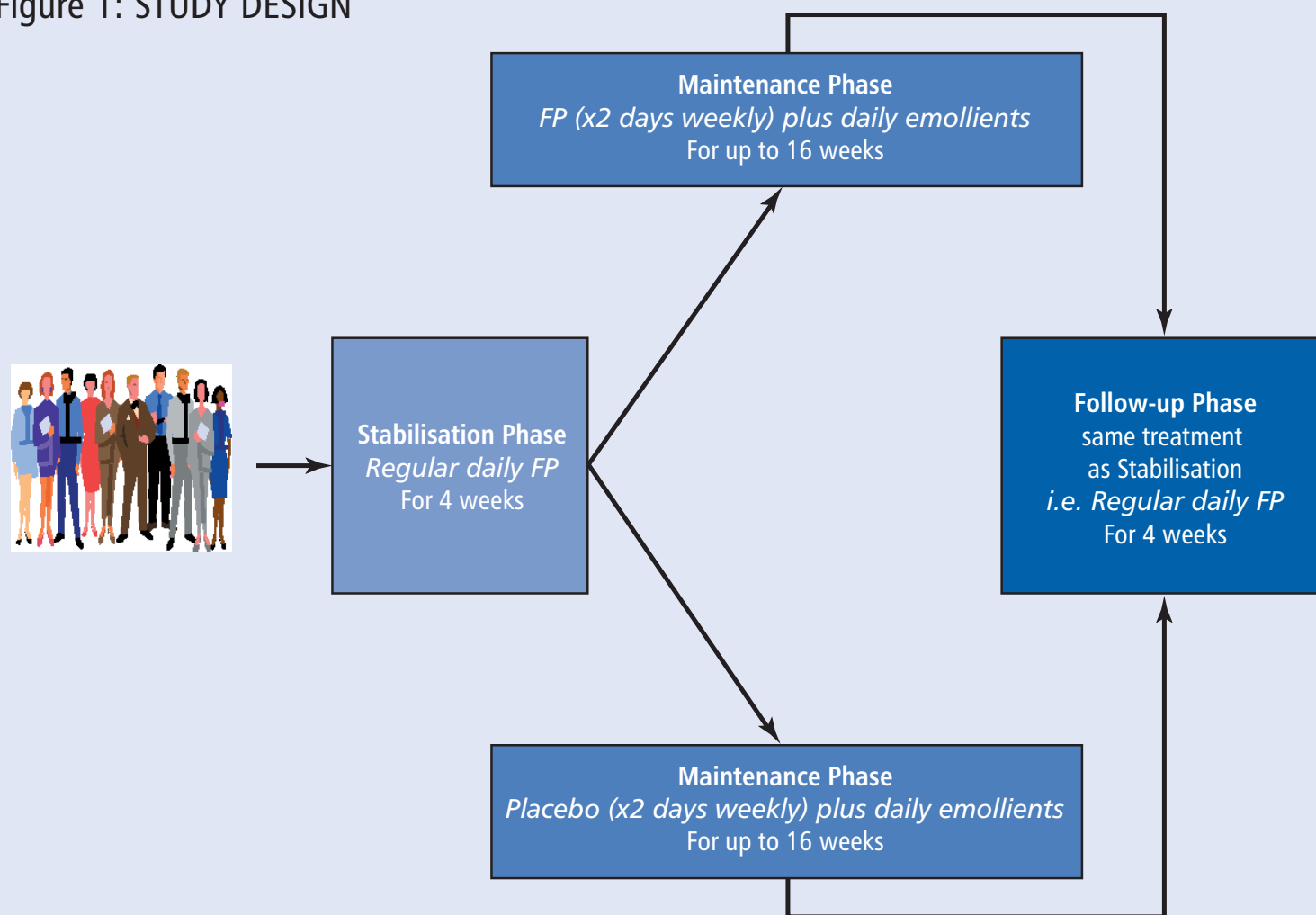
Topical corticosteroids (TCS) are the mainstay of treatment for atopic dermatitis (AD) and can be used safely and effectively if guidelines are followed. Tachyphylaxis (a trend for effectiveness to diminish progressively with continued use) and rebound effects (a flare in disease activity above baseline severity when treatment is withdrawn) have been observed with long term use of the more potent TCS. Most clinical trials of TCS have focused on their short term effects and so very few data are available on effects of their medium to longer term use.

However, four recent controlled studies involving a total of 950 subjects (613 adults, 337 paediatrics) demonstrated that following initial stabilisation of an acute flare, chronic recurrent AD can be managed successfully in the longer term with intermittent twice weekly dosing regimens of fluticasone propionate (FP) plus regular daily emollients (1 - 4). Most of these studies lasted around 20 weeks and in one study safety data were collected for up to 52 weeks.

While none of the studies directly addressed the issue of tachyphylaxis and rebound, the study design of one of them (Berth-Jones et al, 2003) provided follow-up information on all patients who experienced a flare following long term treatment on intermittent therapy. These subjects were re-treated with a further 4-week course of FP (Figure 1). This has enabled a retrospective assessment to be made of the possible presence of tachyphylaxis. In addition, the dose reduction from daily to intermittent therapy has facilitated an assessment of rebound effects.

METHODS

Figure 1: STUDY DESIGN



- The study involved 376 subjects (12-65 years) recruited from 39 dermatology clinics in 6 European countries.
- The presenting acute episode of AD (protocol-defined) was first stabilised with regular twice daily FP Cream or Ointment applied for four weeks. Subjects who were controlled after this period (according to protocol defined criteria) entered a double blind Maintenance phase during which time the application frequency of FP (or placebo) was stepped down to a twice weekly application on two consecutive days for up to 16 weeks. All subjects routinely applied emollient and used bath oil as necessary.
- Those who suffered a relapse (protocol-defined) in the Maintenance phase on intermittent FP (or placebo) therapy entered a Follow-up phase and repeated the same FP treatment as they had received in the Stabilisation Phase.
- This Follow-up phase when subjects were re-treated with daily FP therapy enabled an assessment to be made of the possible presence of tachyphylaxis. In addition, Objective SCORAD data from these subjects were reviewed to assess the possibility of rebound effects.

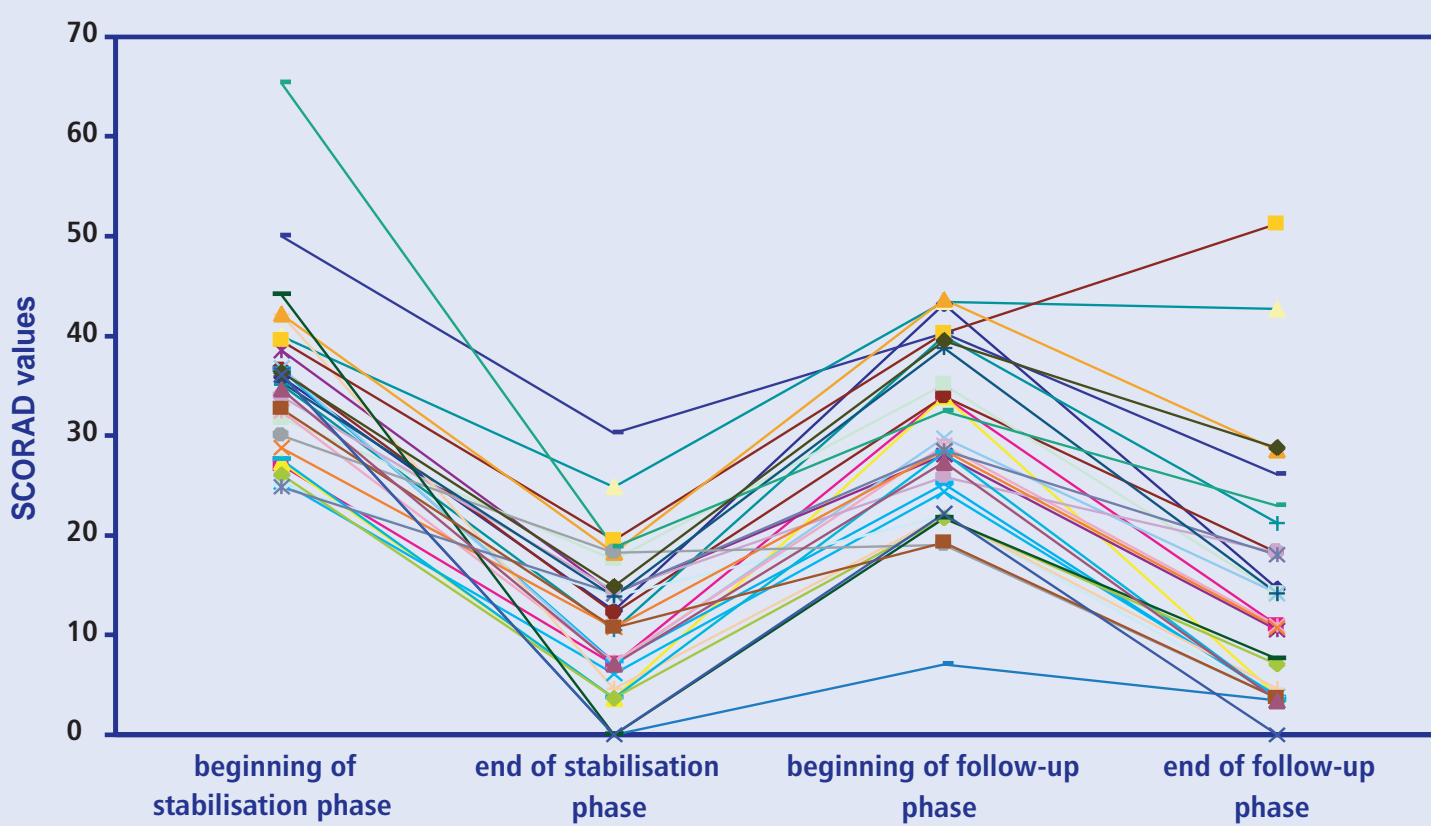
Objective SCORAD

For Objective SCORAD, physicians score both the extent and severity of AD. For extent, a modified 'rule of nines' system is used. For severity, six symptom/signs (oedema/papulation, excoriations, oozing/crusting, lichenification and dryness) are scored from a 0-3 scale. The Objective SCORAD is calculated as: $(0.2 \times \text{extent}) + (3.5 \times \text{severity score})$ and overall AD severity can be defined as

- 0 = no evidence of AD
- >0-15 = mild AD
- >15-40 = moderate AD
- >40 = severe to very severe AD (maximum value achievable = 83).

RESULTS

Figure 2: SCORAD values from first and second relapse (n=31) (relapses occurred at beginning of stabilisation phase and beginning of follow-up phase)



N.B. subjects received daily FP for 4 weeks in the Stabilisation phase followed by intermittent twice weekly FP for up to 16 weeks in a Maintenance phase. Those who relapsed during the Maintenance phase then received daily FP for 4 weeks in a Follow-up phase.

Table 1: Subjects who received FP and who had follow up data during a second relapse (n=31)

	median	range
Data from Initial (presenting) AD flare		
Pre-treatment (i.e. baseline)	35	25 - 65
Post FP treatment (i.e. after 4 wks daily therapy)	11	0 - 30
Data from Second (follow-up) AD flare		
Prior to re-treatment (i.e. at time of relapse)	28	7 - 44
Post FP re-treatment (i.e. 2nd 4 wk course of FP)	11	0 - 51

- Of the 376 subjects involved in the study, 31 had a relapse on long term intermittent FP maintenance therapy.
- SCORAD data from these 31 subjects showed that the intensity of this relapse (beginning of the Follow-up phase) on FP was of a similar magnitude to that of the presenting relapse (beginning of the Stabilisation phase). Therefore, these data provide strong support that there were no rebound effects associated with withdrawal of FP treatment (these subjects had received FP daily for four

weeks in the Stabilisation phase followed by a dose reduction to twice weekly FP therapy for up to 16 weeks in the Maintenance phase).

- SCORAD data from 30 of the 31 (97%) subjects who experienced a relapse on intermittent FP therapy and were re-treated with daily FP, showed that the second course of treatment was highly effective in treating the exacerbation. Therefore, there was no suggestion of tachyphylaxis.

- One subject, a 52 year old female, who had suffered with AD for more than 5 years, responded well to the initial stabilisation treatment and for 10 weeks was controlled with intermittent twice weekly FP maintenance treatment. However, while the subject showed no evidence of rebound effects, she did not respond as well as the others to the second course of FP.

CONCLUSIONS

- Of the 376 subjects involved in the study, 31 suffered a relapse during long term, maintenance treatment on twice weekly FP therapy. The majority did not relapse and were well maintained

- For these 31 subjects, inspection of their SCORAD data showed that the intensity of this relapse following dose reduction was of no greater magnitude than that of the presenting relapse. Therefore, there was no suggestion of rebound effects associated with FP use.

- In addition, a review of the Objective SCORAD values after re-treatment with a second course of FP showed that the majority of subjects responded well to repeated FP use and there was no suggestion of diminished efficacy and therefore no indication of tachyphylaxis.

ACKNOWLEDGEMENTS

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References

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