Review: Clinical Trial Outcome

CLINICAL INVESTIGATION

Long-term management of atopic dermatitis: evidence from recent clinical trials

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Atopic dermatitis (AD) is a superficial itchy inflammation of the skin, which often has a prolonged course. Treatment of AD has been based mainly on topical corticosteroids. When these treatments have proved unsatisfactory, other treatments such as ultraviolet or immunosuppressive treatments have been added. Recently, topical calcineurin inhibitors have also shown efficacy as monotherapy of AD. Many therapies have been shown to be effective in short-term treatments of a few weeks; however, long-term treatment studies of at least 3 months are much less common. In this article we focus on recent long-term efficacy and safety studies. Maintenance treatment of AD has shown its superiority to standard flare treatment both with corticosteroids and topical calcineurin inhibitors. At present it is not clear whether long-term safety hazards associated with AD are due to AD itself or treatments used over time. To clarify this issue, we have reviewed the epidemiological and case–control data on AD, its long-term treatments and cancer.

Keywords: atopic dermatitis • corticosteroid • disease flare • maintenance treatment • monotherapy • standard flare treatment • topical calcineurin inhibitor

Atopic dermatitis (AD) is a superficial itchy inflammation of the skin, which often starts in early childhood. Some patients show spontaneous improvement, whereas in some patients the course is prolonged and can last throughout life. AD affects patients all over the world by reducing their quality of life. AD also has a high socio-economic impact. It is a clinical diagnosis, which is based on the criteria suggested by Hanifin and Rajka [1]. In this classification patients are included that show no signs of sensitization to environmental antigens. This is in contrast to a recent classification that suggests that AD is a disease of sensitization and hence raised immunoglobulin E (IgE) levels play a central role [2]. AD is often accompanied by other atopic manifestations such as rhinitis, asthma and ocular disease. It seems that AD is a risk factor for other atopic diseases, probably through the impaired barrier function of the skin, which allows environmental compounds to penetrate.

■ Proper function of the skin barrier is the primary treatment target in AD

Atopic dermatitis is associated with a superficial inflammation that extends to the normal-looking dry skin [3]. Until recently the aim of treatment consisted of treating disease flares as effectively as possible. New knowledge regarding the poor barrier function in AD has put the emphasis on trying to regain barrier function to a degree that is possible for the respective patient. Filaggrin protein seems to be one of the major components of the skin barrier [4]. Recent studies have shown that nonfunctional mutations of the filaggrin genes are a major risk factor for AD, especially in patients with signs of sensitization to environmental

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antigens [5]. In Europe, approximately 30% of such patients have nonfunctional mutations of the filaggrin gene [6]. Similar nonfunctional mutations of the filaggrin gene have been detected in different parts of the world. One study suggests that patients with normal filaggrin genes can show a decrease in filaggrin protein levels in the skin at sites of active AD [7]. Taken together, present knowledge suggests that treatment of inflammation in AD leads to an improved barrier function of the skin (Figure 1). Some efficacy has been shown with emollients and barrier creams resembling normal components of the skin barrier [8,9]. However, without simultaneous treatment of the inflammation, the results have been modest.

Until approximately 10 years ago, treatment of the skin inflammation in AD consisted mainly of topical glucocorticosteroids, which were used mainly for short periods of a few weeks. When the current disease flare had been treated, further treatment consisted mainly of daily use of emollients until the next flare occurred. Addition of antihistamines or antimicrobials or both have not shown a significant effect in controlled studies [10–12]. In clinical practice, flare treatment often starts with a lag-time of several days or weeks. This results in poor barrier function of the skin, especially in patients with widespread AD and frequent disease flares. Therefore it would be logical to use continuous rather than intermittent long-term treatment. The main obstacles for this treatment modality have been the known long-term adverse events caused by corticosteroids and the possible long-term immunosuppressive effects of calcineurin inhibitors. Studies have been performed with some topical corticosteroids for up to 24 weeks and with topical calcineurin inhibitors (TCIs) for up to 1 year [13–16]. When various clinical studies are compared, the baseline severity of AD is of major importance, as severe dermatitis is clearly more difficult to treat than moderate or mild dermatitis.

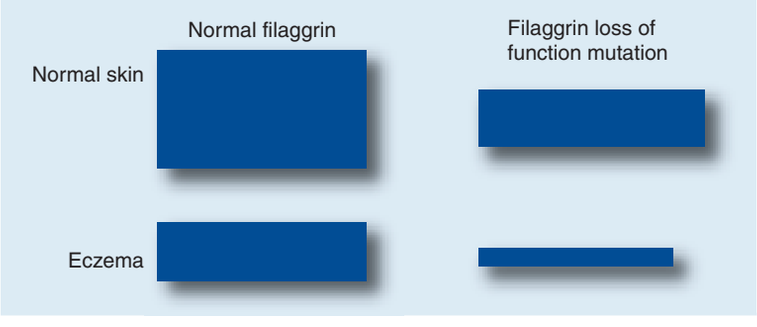

Figure 1. Effective treatment of atopic dermatitis leads to improved filaggrin protein levels in patients with atopic dermatitis.
Data taken from [7].

Long-term topical treatment

Topical corticosteroids have been the first-line treatment for AD for almost 60 years. Nevertheless, possibly due to the known adverse effect of skin atrophy, long-term studies with topical corticosteroids were lacking. Therefore they have been used until recently as flare treatments only. This has often resulted in poor control, especially in patients with more severe AD.

Standard flare treatment

The need to compare TCIs with the first-line therapy (i.e., topical corticosteroids) in long-term treatment of AD led to three long-term studies [17–19]. These comparative studies together with the maintenance studies are, to our knowledge, the only long-term studies of at least 3 months duration with topical corticosteroids and are reviewed below.

All studies included patients with moderate-to-severe AD. The amount of study medication applied was not limited. The first study (n = 658) compared pimecrolimus cream 1% to triamcinolone acetonide cream 0.1% (for trunk and limbs) plus hydrocortisone acetate cream 1% (for face, neck and intertriginous areas) for 12 months [17]. The median Eczema Area and Severity Index (EASI) scores were lower in the corticosteroid group at all time points, suggesting a better efficacy of the corticosteroids. Premature discontinuation due to lack of efficacy was seen in 36.3% of the pimecrolimus- versus 8.2% of the corticosteroid-treated patients. The study revealed the high number of treatment days with topical cortcosteroids needed to control moderate-to-severe AD, that is, 50% of the patients used topical coricosteroids almost continuously for 1 year. Skin striae suggesting atrophogenic effect of treatment were reported by three patients in the topical corticosteroid group, compared with none in patients in the pimecrolimus group. Pimecrolimus-treated patients reported application site reactions more frequently, such as burning and irritation, but there was no difference in the incidence of skin infections between the groups.

Tacrolimus ointment (0.1%) was compared with a corticosteroid regimen (hydrocortisone butyrate 0.1% for trunk and limbs, and hydrocortisone acetate 1% for head and neck) in a 6-month study (n = 972) [18]. Tacrolimus showed superior efficacy throughout the study. Lack of efficacy was the reason for study discontinuation in 10.7% of patients treated with tacrolimus ointment and 25.6% of patients treated with the corticosteroid regimen. More patients treated with tacrolimus experienced adverse events related to the study treatment (67.6% for tacrolimus vs 42.5% for the corticosteroid regimen). The more frequent adverse events in tacrolimus-treated patients were skin burning, alcohol intolerance, skin tingling, hyperaesthesia and herpes simplex infections.

However, the incidence of herpes simplex infections decreased during the study and was comparable with the topical corticosteroids group at month 6 (tacrolimus 1.3% and topical cortcosteroids 1.0%).

The same treatment regimen as above was applied in a 12-month study (n = 80) [19]. This study revealed superior efficacy for tacrolimus ointment in the treatment of the face and neck at month 12, which was supported by a significantly lower transepidermal water loss at the same time point. Otherwise the difference between the groups was nonsignificant at month 12, although the EASI decrease compared with baseline was 91% for tacrolimus ointment and 79% for the corticosteroid regimen. The median number of treatment days during the 12 months was 255 in the tacrolimus and 327 in the corticosteroid groups. Two of the patients treated with corticosteroids showed signs of skin atrophy – striae and subcutaneous hematomas. Otherwise, adverse events were more common in the tacrolimus-treated patients (100%) than in the corticosteroid-treated patients (85%), mainly due to application-site burning.

■ Maintenance treatment modality

The maintenance treatment modality in AD aims to minimize the skin inflammation by daily application of medication during the stabilization phase and then to reduce AD relapses by intermittent treatment, for example two- or three-times weekly, of usually affected areas during the maintenance phase.

Studies with monotherapy

This treatment regimen was initially shown to be effective in two large studies of 20 weeks' duration, which showed that patients who applied fluticasone propionate cream were six- to eight-times less likely to have a relapse compared with those applying only vehicle [13,14]. The study by Berth-Jones and colleagues reported signs of skin thinning, telangiectasia and striae, in three patients, but the symptoms were considered new in only one patient [14]. In the study by Hanifin and colleagues the function of the hypothalamo–pituitary–adrenal axis was assessed at the end of the study in three of the 16 centers [13]. Possible adrenal suppression due to corticosteroid treatment was detected in two out of 44 patients (4.5%). Otherwise there were no differences in adverse events between the treatment groups [13]. A similar treatment regimen with methylprednisolone aceponate showed superiority to treatment with only emollient and did not show any visual signs of skin atrophy [20].

The maintenance regimen was also effective with topical tacrolimus treatment [15,16]. The median time to the first flare in adults was 142 days in the tacrolimus group versus 15 days in the vehicle group, and in children 173 versus 38 days. The maintenance regimen did not increase the total usage of ointment and improved quality of life in adults. The incidence of adverse events was similar in the tacrolimus and vehicle groups. These studies led to a change in label for tacrolimus maintenance treatment in the European Union [15,16].

Combination treatments

Topical pimecrolimus has in several long-term studies been shown to be effective in reducing the number of flares needing topical corticosteroid treatment in both adults, children and infants [21–23]. These flare-preventing studies differ from the maintenance regimen in that twice-daily treatment with pimecrolimus was initiated when the first signs of AD appeared and continued until full clearance of the symptoms. The proportion of patients without a flare in these 12-month studies was approximately twice as high in the pimecrolimus group compared with the vehicle group. The incidence of adverse events was similar in the pimecrolimus and vehicle groups.

Flare prevention with moisturizers

In a long-term study of 26 weeks' duration with a urea-containing moisturizer, eczema was first treated with topical beta-methasone valerate 0.1% for 3 weeks and thereafter patients received either a urea-containing moisturizer or no topical treatment at all. The median time to relapse was more than 180 days in the treatment group and 30 days in the untreated group [8]. Various barrier-strengthening creams have been marketed recently. To date, long-term data on their use are not available [9].

■ Long-term systemic treatment

Long-term systemic treatment is usually administered together with topical corticosteroids. In only a few studies has the actual amount of topical corticosteroids been measured. Systemic treatment usually diminishes but does not remove the need for topical corticosteroids. Of the systemic treatments, the most convincing evidence is for cyclosporin, whereas data on azathioprine and methotrexate are scarce [24].

■ Randomized controlled studies

Cyclosporin

Sowden and colleagues performed a double-blind, controlled, crossover study, where cyclosporin was compared with placebo in 33 patients [25]. Patients first received cyclosporin or placebo for 8 weeks and then *vice versa*. Cyclosporin was superior to placebo ($p < 0.001$), but adverse events were seen more often during cyclosporin treatment (in 20 patients) compared with placebo (8 patients). No patient had to be withdrawn owing to adverse events.

12-month ultraviolet therapy

Psoralen plus ultraviolet (UV)A (PUVA) therapy and UVA1 therapy were compared in a randomized observer-blinded study by Tzaneva and colleagues [26]. A total of 40 patients were included in the trial, but only 23 patients completed the crossover treatment. The patients received either 15-times PUVA treatment or UVA1 treatment and in the case of relapse they received 15-times the other treatment option. The patients were followed up for 12 months after the last treatment period. Both treatments reduced the baseline scoring AD (SCORAD) score, but PUVA treatment reduced it significantly more than UVA1. The mean remission period was 4 weeks after UVA1 treatment and 12 weeks after PUVA treatment.

UV therapy versus cyclosporin

Granlund and colleagues performed a randomized, open, controlled study comparing the safety and efficacy of cyclosporin and UVAB therapy [27]. A total of 72 patients were randomized (36 in each group) to receive either cyclosporin or UVAB for 1 year of intermittent therapy. Cyclosporin produced significantly more days in remission during the 1-year study. A significant increase in serum creatinine was observed in two patients and seven patients developed mild or moderate hypertension during the cyclosporin treatment.

Azathioprine

Berth-Jones and coworkers performed a double-blind, placebo-controlled, crossover trial with azathioprine versus placebo [28]. Each treatment period was 3 months in duration. A total of 37 patients were enrolled in the study, 16 patients were withdrawn (43%): 12 during azathioprine treatment and four during placebo treatment. The six area, six sign AD (SASSAD) score fell by 26% in patients on azathioprine compared with 3% on placebo. However, the results are difficult to interpret because of the large number of dropouts during the study. No significant reduction of itch could be found with azathioprine.

Another double-blind, randomized, controlled trial with azathioprine versus placebo was performed in 63 patients for 12 weeks [29]. In total, 54 patients (86%) completed the study. Topical corticosteroids (hydrocortisone and beta-methasone) were allowed during the study. At week 12, there was a 37% improvement in disease activity in the azathioprine-treated patients compared with 20% in the placebo group.

Antihistamines

The role of antihistamines in AD is adjunctive. The efficacy shown in some studies is probably due to the sedation caused by these agents. Nonsedating antihistamines have not shown efficacy in controlled studies [10].

Uncontrolled studies

Cyclosporin

Berth-Jones and coworkers performed an open, multicenter study with cyclosporin in patients with AD [30]. A total of 100 patients were included in the study and 65 completed the 48 weeks of treatment. Of the withdrawals, seven were determine to probably be caused by treatment. Cyclosporin produced rapid improvement in disease activity. Most patients relapsed during the follow-up period of 8 weeks, but not to baseline severity.

UV therapy

The long-term efficacy of UVA1 phototherapy was studied by Abeck and colleagues [31]. A total of 32 patients underwent UVA1 therapy daily for 3 weeks (15 times) and the patients were followed up for 3 months. After 1 month of treatment a significant skin improvement was still present, but at the end of the 3 months follow-up the skin condition had reached the pretreatment level. The effectiveness of UVA1 therapy seems to be merely short term.

Methotrexate

A retrospective study with 20 patients was reported by Lyakhovitsky and colleagues [32]. The patients had moderate-to-severe AD and received methotrexate once weekly (dose: 10–25 mg) with folic acid supply during a period of at least 8–12 months. Treatment response was seen in 16 patients. The mean SCORAD decreased by 44.3%. The first improvement was observed after a period ranging from 2 weeks up to 3 months. Nausea and elevation of liver enzymes was observed in five patients.

An open-label study in 12 patients using methotrexate for 24 weeks was performed by Weatherhead and colleagues [33]. The treatment started with 10 mg once weekly and the dose was increased weekly with 2.5 mg until response or adverse events. The patients were followed up for 12 weeks after stopping treatment. Unrestricted use of standard topical therapy was permitted. An improvement in disease activity by 52% from baseline was observed. One patient withdrew from the study owing to adverse events. In eight patients a persistent improvement was seen 12 weeks after stopping methotrexate.

Mycophenolate mofetil

In an open study by Neuber and coworkers ten patients with severe AD were treated with mycophenolate mofetil for a total of 12 weeks, 1 week with 1 g once daily and 11 weeks with 2 g once daily [34]. No patient discontinued because of lack of efficacy. In these patients, mycophenolate mofetil was effective at a dose of 2 g once daily. There was a positive effect on serum IgE levels. The relevance of elevated IgE in patients is not understood, but it has been suggested that there is a role of IgE in the pathogenesis of

AD [35]. This is supported by a clear correlation between disease severity and IgE levels [36].

■ Long-term safety studies

All published long-term safety studies of more than 1 year have been uncontrolled. However, the new cancer studies are largely case–control studies with large populations of up to millions of patients and controls.

Infections

Large uncontrolled long-term safety studies have been published on tacrolimus treatment for up to 4 years. All of these studies show a decrease in skin infections over time [37,38]. Reduction of bacterial colonization rates by *Staphylococcus aureus* has been shown with various treatments. With tacrolimus ointment this has also been shown in a long-term study of 12 months [39].

Cancer

Earlier studies on AD and cancer were performed mainly with hospital-based patients. As these patients usually have more severe forms of AD, such patients would also be prone to receive systemic immunosuppressive or UV treatments. The earlier studies do not reveal any treatments used. An increased risk for skin cancer for AD patients has been detected in one study [40]. A recent study has revealed an increased incidence of lymphoma in AD in an age-adjusted case–control study [41].

In recent years there have been attempts to evaluate the risk of cancer associated with various treatments. No increased risk for skin cancer or lymphoma has been observed with topical tacrolimus treatment [42,43]. Two human studies have not revealed any increased risk for skin cancer in patients treated with TCIs including tacrolimus ointment and pimecrolimus cream [44,45]. One large case–control study showed a slightly increased risk for lymphoma associated with severe AD and topical use of potent corticosteroids but not with TCIs, which showed a decreased risk [46]. One study suggested an increased risk for topical tacrolimus of one specific type of lymphoma, namely T-cell lymphoma of the skin [47]. This study also revealed the difficulty in the diagnosis of early T-cell lymphomas of the skin, as several cases were retracted after chart review, as the lymphoma had appeared before treatment with TCIs. One recent study showed a slightly increased risk for lymphoma in both corticosteroid- and topical calcineurin-treated patients compared with the general population, but there was no difference between the various treatments [48]. Taken together, it seems that AD, as such, may be associated with a risk for lymphoma, which might be related more to the severity of AD than the topical treatments used.

Future perspective

Maintenance treatment of AD has improved the long-term outcome, especially in the more severe forms of the disease. This treatment modality should become the major form of AD treatment. This treatment modality better suits TCIs than topical corticosteroids, as there are no long-term harmful effects on the skin barrier [4]. The ultimate goal should be complete control of AD. Uncontrolled follow-up studies with tacrolimus ointment have revealed that such treatment can decrease not only disease severity but also have beneficial long-term effects on serum IgE levels. Evidence from long-term studies with tacrolimus ointment suggests that effective long-term anti-inflammatory treatment of AD results in elimination of staphylococci, a shift in the skin inflammation towards Th1 dominance and a normalization of the skin barrier function [39,49–52]. Effective, long-term treatment of AD may also improve respiratory symptoms [53,54]. For flare prevention, pimecrolimus may be useful for

Executive summary

- Atopic dermatitis (AD) is an itchy disease that is influenced by inherited and environmental factors.
- The main treatments of AD are topical monotherapies with corticosteroids or calcineurin inhibitors.
- The target treatment is to improve skin barrier function. This is achieved mainly by anti-inflammatory treatments. Filaggrin protein is of major importance for the barrier function of the skin. Many patients have loss-of-function of filaggrin genes, which results in low filaggrin protein levels.
- Baseline severity of AD is of major importance when various studies are compared. For treatment outcome, different subjective and objective parameters have been assessed.
- Earlier treatments mainly involved treatment of flares. Maintenance treatment twice weekly prevents flares effectively. These treatments have been tried for corticosteroids for up to 24 weeks and for topical calcineurin inhibitors for 1 year. Tacrolimus ointment has been used as monotherapy and pimecrolimus mainly together with topical corticosteroids.
- Cyclosporin is the systemic treatment most extensively studied, although azathioprine and methotrexate can be useful in selected patients. Long-term treatment with ultraviolet is poorly studied.
- Long-term safety studies do not show an increase of infections with topical calcineurin inhibitors. Steroid safety is not well studied over the long-term.
- Conflicting reports have been published on AD and cancer. Patients with AD (and especially severe AD) may have a higher incidence of lymphoma compared with the normal population. A possible role of treatment needs further study.

long-term maintenance treatment of less severe forms of AD. The role of corticosteroids will be mainly on short-term control of disease flares. Systemic treatment and UV treatments will be used less in future years.

When TCIs are used, monotherapy without corticosteroids should be used whenever possible, as the long-term outcome may be worsened by mixing these compounds [55]. Some body regions, such as the hands, feet and scalp, will also need additional corticosteroid treatment in the future. Long-term treatment results are greatly influenced by patient compliance, and better information for patients will improve this. The long-term outcome for individual patients can usually already be estimated after 1 year of treatment [54]. Patients with good compliance can expect an improvement of all atopic symptoms over time. In future, treatment will be started in early infancy after the initial appearance of AD.

Is there a possibility to improve the barrier function of the skin with other compounds? Emollients and barrier creams may improve due to extensive research. Possible new topical anti-inflammatory compounds could be in the pipelines of drug companies.

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■■ **Important large case–control study to show that severe dermatitis rather than treatments is the major risk factor for lymphoma in AD.**

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