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Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry

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Conflicts of interest
None declared.

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Summary

Background Few studies have directly compared the clinical efficacy of psoralen plus ultraviolet A (PUVA) vs. biologics in the treatment of psoriasis.

Objectives To compare the clinical efficacy of PUVA and biologic therapies for psoriasis under daily life conditions.

Methods Data from a psoriasis registry (http://www.psoriasis-therapieregister.at) of 172 adult patients with moderate to severe chronic plaque psoriasis treated between 2003 and 2010 were analysed retrospectively. These patients had received oral PUVA [118 treatment courses including 5-methoxypsoralen (5-MOP; n = 32) and 8-methoxypsoralen (8-MOP; n = 86)] and/or biologic agents [130 treatment courses including adalimumab (n = 18), alefacept (n = 32), efalizumab (n = 17), etanercept (n = 38), infliximab (n = 7) and ustekinumab (n = 18)]. Treatment responses were analysed in terms of Psoriasis Area and Severity Index (PASI) improvement, including complete remission (CR) and reduction of PASI by at least 90% (PASI 90) or 75% (PASI 75), at treatment completion for PUVA (median time 10·3 and 9·2 weeks, for 8-MOP and 5-MOP, respectively) and at week 12 for biologics.

Results Intention-to-treat–as observed CR, PASI 90 and PASI 75 rate was 22%, 69% and 86% for PUVA compared with 6%, 22% and 56% for adalimumab ($P = 0{\cdot}0034$ by adapted Wilcoxon test), 3%, 3% and 25% for alefacept ($P = 0{\cdot}000000002$), 6%, 6% and 59% for efalizumab ($P = 0{\cdot}000053$), 6%, 29% and 39% for etanercept ($P = 0{\cdot}0000086$), 29%, 71% and 100% for infliximab ($P = 0{\cdot}36$) and 6%, 39% and 67% for ustekinumab ($P = 0{\cdot}028$). When applying a more conservative *post-hoc* modified worst-case scenario analysis, with CR of 15%, PASI 90 of 58% and PASI 75 of 69%, PUVA was superior only to alefacept ($P = 0{\cdot}000013$), efalizumab ($P = 0{\cdot}015$) and etanercept ($P = 0{\cdot}0037$). There were no statistically significant differences in PASI reduction rates between PUVA and infliximab.

Conclusions Retrospective analysis of registry data revealed that the primary efficacy of PUVA was superior to that of certain biologics. Prospective head-to-head studies of PUVA and biologics are warranted to confirm these observations.

Psoralen plus ultraviolet (UV) A (PUVA) photochemotherapy is a long-standing, widely used, and very effective systemic therapy for psoriasis.[1] Yet, the mechanism by which PUVA normalizes psoriatic skin remains poorly understood. Psoralen is known to intercalate between nucleic acids and to induce, upon exposure to UVA radiation, the formation of psoralen-pyrimidine adducts that inhibit DNA synthesis and epidermal proliferation.[2] PUVA is known to have profound biologic-like immunomodulating activity (e.g. the ability to reduce the number and activation of T cells).[2–4] PUVA is also known to reduce the expression of cytokines and chemokines such as interleukin (IL)-22, IL-17, IL-23, IL-8 and tumour necrosis factor-α, and growth factors such as vascular endothelial growth factor and intracellular adhesion molecule-1.[2,5] Very

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recently, we demonstrated in a psoriasis disease model that PUVA can induce IL-10-positive regulatory T cells while simultaneously inhibiting the Th17 helper pathway,[6,7] alterations that may be responsible for the fast and long-lasting reduction of inflammatory and hyperproliferative skin changes in psoriasis observed after PUVA treatment. Meanwhile, better understanding of the immunological basis of psoriasis has led in recent years to the development and introduction of biologic agents that target key steps in the pathogenesis of psoriatic disease and consequently to expansion of the psoriatic armamentarium.[8–22] Nevertheless, clear differences in treatment response have been observed: a single course of antipsoriatic PUVA therapy is often followed by a disease-free interval lasting months, whereas antipsoriatic therapy with other systemic agents (including biologics) is often followed by quick recurrence.

Up to now, few studies have directly compared the clinical efficacy of PUVA vs. other systemic agents (e.g. biologics) in the treatment of psoriasis. We therefore retrospectively analysed all available primary efficacy data for patients treated with various biologics and/or oral PUVA at our institution over a 7-year period since the introduction of biological agents for the treatment of moderate to severe plaque psoriasis.

Patients and methods

Study design

This was an observational retrospective cohort study of clinical data extracted from the Psoriasis Registry, Graz (http://www.psoriasis-therapieregister.at). The study was approved by the local ethics committee of the Medical University of Graz (application number 21-094 ex 09/10) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study setting

The data analysed in this study were collected at the Department of Dermatology, Medical University of Graz, from patients with psoriasis treated regularly with PUVA vs. biologics under daily life conditions outside of clinical trials between January 2003 and February 2010.

Study population

A total of 172 patients (61 women and 111 men) met the criteria for inclusion in the registry and analysis (i.e. ≥ 18 years of age with chronic plaque psoriasis that had been treated with oral PUVA and/or at least one course of a biologic agent). According to guidelines of the Austrian Society of Dermatovenereology and the prerequisites of the Reimbursement Code of the Main Association of the Austrian Social Security Institutions, treatment with a biologic agent is indicated if a patient has moderate to severe chronic plaque psoriasis [defined as ≥ 10% body surface area involvement or Psoriasis Area and Severity Index (PASI) ≥ 10] and has failed is unable to tolerate, or has a contraindication to, conventional systemic therapies such as ciclosporin, methotrexate or PUVA.

Efficacy assessment and data analysis

The endpoints of the study were complete clearance (CR) or reduction of the PASI by at least 90% (PASI 90), 75% (PASI 75) or 50% (PASI 50) in oral PUVA-treated patients at end of treatment or biologic-treated patients at week 12 of biologic therapy. The Psoriasis Registry, Graz contains data on PASI and specific PASI reduction categories (i.e. CR, PASI 90, PASI 75 and PASI 50) at defined time points (i.e. at the end of PUVA therapy, after 12 weeks of biologic therapy, and thereafter at regular intervals) for all patients treated at the Department of Dermatology. For this retrospective study, data on patient characteristics and clinical PASI reduction categories were extracted from the electronic databank of the Psoriasis Registry, Graz. The percentages of patients achieving specific PASI reductions at the end of PUVA therapy or at week 12 of treatment with specific biologic agents were determined.

Statistical analysis

Treatment efficacy in patients was compared according to a score for PASI reduction: 1 for CR, 2 for 90% to < 100%, 3 for 75% to < 90% and 4 for < 75% reduction. Each biologic was compared with PUVA using the exact Wilcoxon test on that score. As there were patients who underwent more than one treatment cycle, scores from individual treatments were not independent and the test had to be adapted.[23] R 2.12.1 and the package coin were used for calculations (http://www.r-project.org).

Results

Patient characteristics

The flow charts in Figure 1 show the number of patients and the number of treatment courses available for retrospective analysis. A total of 194 patients was assessed for eligibility. After exclusion of 22 patients with missing response data, there remained for statistical analysis a total of 172 patients who underwent a total of 248 treatment courses. Of those patients, 64 had received oral PUVA, 96 had received a biological agent, and 12 had received both oral PUVA and a biological agent for a minimum duration of 3 months (Fig. 1). All patients analysed in this study had received standard PUVA [most often after testing for individual minimal phototoxicity dose (MPD)] two to four times per week and/or standard biologic therapy.

At the start of a treatment course, the mean ± SD age of patients treated with PUVA or a biologic was 48·5 ± 15·7 and 46·2 ± 11·8 years; the mean ± SD duration of disease was 23·4 ± 11·9 and 22·9 ± 10·5 years; and the mean ± SD PASI was 15·0 ± 4·0 and 16·9 ± 7·3, respectively. The determination of outcome in patients who received systemic monotherapy

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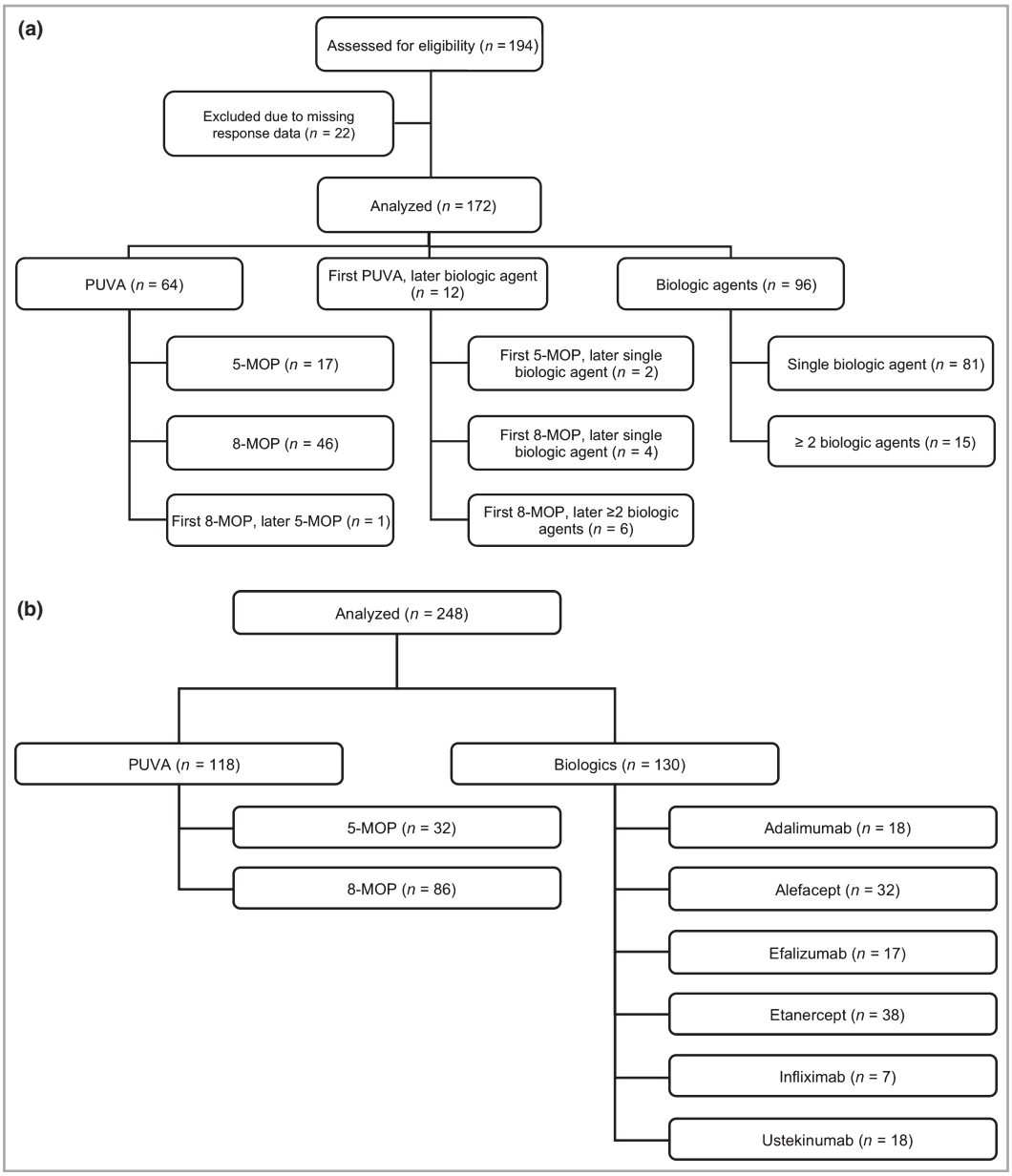

Fig 1. Flow charts showing numbers of (a) patients and (b) treatment courses. PUVA, psoralen plus ultraviolet A; MOP, methoxypsoralen.

(either PUVA or biologic) was the primary objective of this study. Fifteen patients who had been treated with oral 8-methoxypsoralen (8-MOP) + UVA and 10 patients who had been treated with oral 5-methoxypsoralen (5-MOP) + UVA had also received concomitant oral acitretin treatment.[24] Therefore, these patients were included in the final analysis; however, in keeping with the primary objective of the study, the outcome for these patients was set in an intention-to-treat–worst-case scenario analysis as PUVA monotherapy failure (i.e. PASI < 50).

Efficacy

Clinical efficacy was assessed for PUVA at the end of treatment (a median of 10·3 and 9·2 weeks for 8-MOP and 5-MOP, respectively) and for biologics after 12 weeks of treatment. The total number of treatment courses and the percentages of those treatment courses that resulted in CR, PASI 90, PASI 75 and PASI 50 are analysed in Table 1. Because 8-MOP and 5-MOP had similar clinical efficacy (without statistical difference), the data for patients so treated were pooled for comparisons of PUVA vs. biologic therapies. The results of the analysis are presented in Table 1. For PUVA treatment courses, the intention-to-treat–as observed rates (including the response in 25 patients treated with concomitant oral acitretin) of CR, PASI 90 and PASI 75 were 22%, 69% and 86%. These PUVA rates were statistically superior to those of alefacept, efalizumab, adalimumab, etanercept and ustekinumab (Table 1). Similar or even higher statistical significances were received in the per-protocol analysis comparing PUVA vs. each

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Table 1 Psoriasis Area and Severity Index (PASI) reduction in psoralen plus ultraviolet (UV) A (PUVA) vs. biologic treatment courses

Treatment	Total number of treatment courses	Number (%) of patients with category of PASI reduction				
		CR[a]	PASI 90[a]	PASI 75[a]	PASI 50[a]	P-value[b]
Oral 8-MOP + UVA						
ITT–as observed[c]	86	20 (23)	59 (69)	77 (90)	79 (92)	–
ITT–worst case[d]	86	15 (17)	50 (58)	63 (73)	65 (76)	–
Per-protocol[e]	71	15 (21)	50 (70)	63 (89)	65 (92)	–
Oral 5-MOP + UVA						
ITT–as observed[c]	32	6 (19)	23 (72)	24 (75)	26 (81)	–
ITT–worst case[d]	32	3 (9)	19 (59)	19 (59)	19 (59)	–
Per-protocol[e]	22	3 (14)	19 (86)	19 (86)	19 (86)	–
Total PUVA						
ITT–as observed[c]	118	26 (22)	82 (69)	101 (86)	105 (89)	–
ITT–worst case[d]	118	18 (15)	69 (58)	82 (69)	84 (71)	–
Per-protocol[e]	93	18 (19)	69 (74)	82 (88)	84 (90)	–
Biologics[c]						
Adalimumab	18	1 (6)	4 (22)	10 (56)	13 (72)	0·0034
Alefacept	32	1 (3)	1 (3)	8 (25)	20 (63)	0·000000002
Efalizumab	17	1 (6)	1 (6)	10 (59)	13 (76)	0·000053
Etanercept	38	2 (6)	11 (29)	15 (39)	32 (84)	0·0000086
Infliximab	7	2 (29)	5 (71)	7 (100)	7 (100)	0·36
Ustekinumab	18	1 (6)	7 (39)	12 (67)	16 (89)	0·028
All biologics	130	NA	NA	NA	NA	NA

CR, complete remission; PASI 90, PASI 75 or PASI 50, reduction of PASI by at least 90%, 75% or 50%, respectively, from start of treatment; MOP, methoxypsoralen; ITT, intention-to-treat; NA, not appropriate. [a]At week 12 for biologics and at treatment completion for PUVA. [b]P-values refer to the exact Wilcoxon test and compare the ITT–as observed rates of the most relevant PASI reduction categories (i.e. CR, PASI 90 and PASI 75) taken together and observed after treatment with each biologic vs. PUVA. [c]ITT–as observed: ITT analysis was done with data as observed, including the actual PASI reduction response from 25 patients receiving concomitant oral acitretin. [d]ITT–worst case: ITT analysis with worst-case scenario by setting the response of patients receiving concomitant oral acitretin as PUVA monotherapy failure (i.e. PASI < 50), irrespective of the actual PASI reduction. [e]Per-protocol: per-protocol analysis of patients treated with PUVA, excluding all patients receiving concomitant oral acitretin.

biologic (P-values not shown). When applying a more conservative *post-hoc* modified worst-case scenario analysis, with CR of 15%, PASI 90 of 58% and PASI 75 of 69%, PUVA was superior only to alefacept ($P = 0{\cdot}000013$), efalizumab ($P = 0{\cdot}015$) and etanercept ($P = 0{\cdot}0037$) (Fig. 2). The PASI < 50% reduction intention-to-treat–worst-case scenario rate (PASI < 50) of 29% (34/118) included the outcome for the 25 patients (21%) who had been treated with concomitant oral acitretin set as PUVA monotherapy failure, irrespective of actual PASI reduction category. There were no statistically significant differences in PASI reduction rates between PUVA and infliximab and there was no statistically significant difference in PASI 50 rates between PUVA and any biologic therapy.

Discussion

Safe, effective therapies for chronic plaque psoriasis are sorely needed. Antipsoriatic biologic therapies have been shown to be clinically efficacious in numerous double-blinded, placebo-controlled trials.[8–22] PUVA therapy has been shown to be very effective in large multicentre studies in PUVA-treated patients, one from Europe ($n = 3175$) and one from the U.S.A. ($n = 1308$).[25,26] In both PUVA studies, at least 88% of patients experienced psoriatic skin clearing. Only one randomized placebo-controlled interindividual trial has demonstrated the efficacy of PUVA therapy using PASI scoring. In that study, per-protocol analysis showed that 86% (18/21) of PUVA-treated patients achieved PASI 75 after 12 weeks of treatment.[27] We have shown in an intraindividual trial using different dosing regimens and weekly testing for MPD that PUVA-treated patients achieved PASI 75 in 89% (16/18) and CR in 83% (15/18) of cases, irrespective of the PUVA treatment regimen used (i.e. 0·5 MPD four times a week vs. 1 MPD twice per week; or 0·5 MPD twice per week vs. 0·75 MPD twice per week).[28] However, biologics and PUVA have not been compared head-to-head in blinded, placebo-controlled trials. Such comparative blinded studies are difficult as PUVA therapy induces erythema and pigmentation.

Our present retrospective analysis was an attempt to address this difficulty. We found that the efficacy of PUVA administered under daily life conditions at our clinic fell within the efficacy range established by the clinical studies discussed above.[25–28] In fact, a per-protocol-type analysis of PUVA efficacy in the present study (i.e. analysis that excluded the 25 courses of concomitant oral acitretin treatment) revealed CR, PASI 90 and PASI 75 rates of 19% (18/93), 74% (69/93) and

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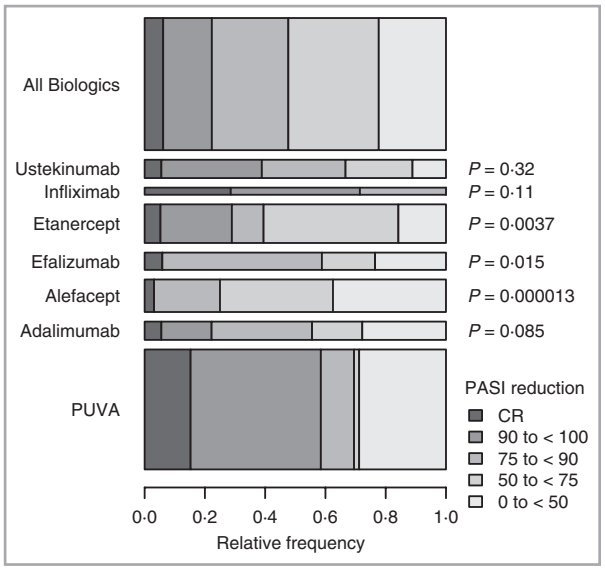

Fig 2. Psoriasis Area and Severity Index (PASI) reduction in patients treated with psoralen plus ultraviolet A (PUVA) vs. biologic therapy. Horizontal extension of bars represents the relative frequency of treatment results (PASI reduction) in PUVA-treated vs. biologic-treated patients. The height of the bars is proportional to the number of patients who received the treatment. P-values refer to the exact Wilcoxon test based on adjusted patient frequencies and compare the most relevant PASI reduction categories [i.e. complete remission (CR), PASI 90 and PASI 75] taken together and observed after treatment with each biologic vs. PUVA. Data presentation of analysis is by intention-to-treat with worst-case scenario (for details see footnote to Table 1 and Results).

88% (82/93), respectively (Table 1). Similar rates were observed in the intention-to-treat–as observed analysis. Likewise, the efficacy of biologics administered under daily life conditions at our clinic also compared well with that in previously reported controlled clinical trials. For instance, Gordon *et al.*[8] observed PASI 75 reduction at week 12 in 53% of patients taking adalimumab at a standard dose of 40 mg subcutaneously (s.c.) every other week (vs. 56% in our present study). Griffiths *et al.*[11] reported a PASI 75 reduction at week 12 in 67·5% of patients who received 45 mg of ustekinumab (at week 0 and 4) and 56·8% of those who received etanercept at a dose of 50 mg twice weekly (vs. 67% for ustekinumab and 39% for etanercept in our present study). The lower response rate for etanercept seen in our retrospective analysis may be attributed to the fact that most patients received a median dose of 25 mg s.c. twice weekly, a dosage that has been reported to result in PASI 75 rates of 30–34% at week 12.[10,15,19] Others have reported PASI 75 reduction in approximately 30% of patients receiving alefacept weekly[29] (compared with 25% in our present study).

The aim of our retrospective analysis was to compare the relative effectiveness of oral PUVA vs. biologics in terms of PASI reduction. Considering CR, PASI 90 and PASI 75 reduction rates together, our analysis suggests that PUVA administered under daily life conditions is a more effective antipsoriatic therapy than certain biologics, including etanercept, efalizumab and alefacept, and possibly also adalimumab and ustekinumab, and equally effective as infliximab, at least after week 12 of treatment (Table 1, Fig. 2).

However, our retrospective data analysis has several limitations. First, no definitive comparison of PASI reduction between PUVA and biologic modalities is warranted because (i) it would not be based on a head-to-head comparison of PUVA and biologics; and (ii) the small number of patients treated with certain biologics, in particular infliximab, makes definitive comparisons impossible. Second, the clinical responses to PUVA and biologics were evaluated at different time points. For PUVA, PASI reduction was calculated at the time of maximum response (i.e. 10·3 and 9·2 weeks for the treatment with 8-MOP and 5-MOP, respectively). Nevertheless, the mean treatment duration of PUVA therapy in our patients correlated well with the mean treatment durations published in the literature. For instance, Stern[2] reported that clearing of psoriasis required about 24 PUVA treatments and that remissions lasted 3–6 months. For biologic therapies, PASI reduction was calculated after 12 weeks even though the maximum response to biologic therapy sometimes occurs later, as for instance reported for adalimumab,[17,21] etanercept[10] or alefacept.[12,13] Third, the mean PASI at start of therapy differed for PUVA vs. biologics (15·0 vs. 16·9). However, we did not consider this difference to have much of a restrictive effect on our analysis as, in our experience, it is usually easy to achieve a significant reduction in initially higher PASI scores.

The clinical efficacy rates for both PUVA and biologic therapy achieved under real-life conditions (as documented in our institution's psoriasis registry and revealed by our present retrospective analysis) compare favourably with historical data from clinical studies. Our present findings also suggest that the primary efficacy of PUVA is superior to that of certain biologics. Together, these observations warrant prospective, controlled head-to-head trials of PUVA and biologic therapies.

What's already known about this topic?

- Clinical studies have established that both oral psoralen plus ultraviolet A (PUVA) and biologics are very effective against moderate to severe chronic plaque psoriasis.

What does this study add?

- Under daily life conditions, the primary efficacy of oral PUVA is superior to that of certain biologics in moderate to severe chronic plaque psoriasis.

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