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REVIEW ARTICLE

Systemic Combination Treatment for Psoriasis: A Review

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Psoriasis is a chronic inflammatory skin disease, which affects approximately 2.6% of the population in Northern Europe and Scandinavia. To achieve disease control, combinations of systemic treatments are sometimes needed for variable time periods. However, no evidence-based guidelines exist for the use of systemic combination therapy. Therefore, the aim was to review the current literature on systemic anti-psoriatic combination regimens. We searched PubMed, and identified 98 papers describing 116 studies (23 randomized) that reported on the effect of various systemic combination treatments. The most thoroughly investigated combination was retinoid and phototherapy. Further controlled research is needed to define the safest and most effective combination regimens. ***Key words: psoriasis; systemic treatment; combination treatment.***

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Psoriasis is a chronic inflammatory skin disease with an estimated global prevalence ranging from 0.5% to 4.6% (1), and it affects approximately 2.6% of the population in Northern Europe and Scandinavia (2).

Psoriasis vulgaris, the most common form, accounts for more than 80% of psoriasis cases (1). Most patients are mildly affected and can be treated adequately with topical medication, but 10–20% of patients have moderate-to-severe disease and require phototherapy or systemic treatment. Frequently, however, this does not result in adequate disease clearance, and therefore systemic treatments are sometimes combined for variable time periods to achieve an additive or synergistic effect. Dosages of the individual agents may then be reduced to minimize side effects. Also, in patients with moderate-to-severe psoriasis, combination therapy is often administered for shorter time periods while monotherapy is changed from one drug to another.

No evidence-based guidelines exist for the use of systemic combination treatment. The purpose of this study was therefore to review the current literature on systemic anti-psoriatic combination regimens, to provide a readily available summary of studies, in which systemic treatments were combined.

MATERIALS AND METHODS

We searched PubMed up to 31 October 2009 to identify all retrospective and prospective studies, including case reports published in English in which patients with psoriasis received systemic combination treatment. The search string consisted of the following free-text terms: "psoriasis", "combined", "combination", "concurrent", and "concomitant". The Cochrane Controlled Trials Register was searched using the free-text term "psoriasis" and no related Cochrane Systematic Review exists. In addition, a search using the Medical Subject Heading "psoriasis" revealed no relevant studies. Review articles and articles cited in original papers allowed us to identify additional studies. Articles without information on the efficacy of treatment and studies reporting on the effect of sequential and rotational therapy, were excluded. No studies were excluded because of inadequate study design. Studies reporting on the effect on psoriatic arthritis as a primary endpoint were included if information about the effect on the cutaneous manifestations was provided. Combinations involving phototherapy (psoralen plus ultraviolet A (PUVA), narrowband UVB (NB-UVB) and broadband UVB (UVB)) were also included. This search revealed 98 papers describing 116 retro- and prospective studies, of which 23 were randomized.

The studies were sorted into five main groups as follows: (1) methotrexate (MTX) combinations, (2) retinoid combinations, (3) cyclosporine combinations, (4) biological combinations, and (5) other systemic combinations. Within each of these five main groups, studies were subdivided according to which medication the "main" agent was combined with (Fig. 1). In these subgroups, study design, number of patients, treatment regimen and efficacy is shown either in Table I (randomized studies) or in supplementary Table SII (available from http://adv.medicaljournals.se/article/abstract/10.2340.00015555-0905/Tab2) (non-randomized studies). In many cases no clearly defined or objectively determined inclusion criteria were stated, but we assume that the patients had moderate-to-severe psoriasis since combination therapy was initiated. Furthermore, objective assessment, such as Psoriasis Area Severity Index (PASI) score, was frequently missing and instead we listed investigator comments on the effect of treatment. Some studies report on several different combinations and may therefore appear in more than one group.

RESULTS

Combination therapies with methotrexate

We identified 20 studies in which MTX was given in combination with another systemic drug. Six studies

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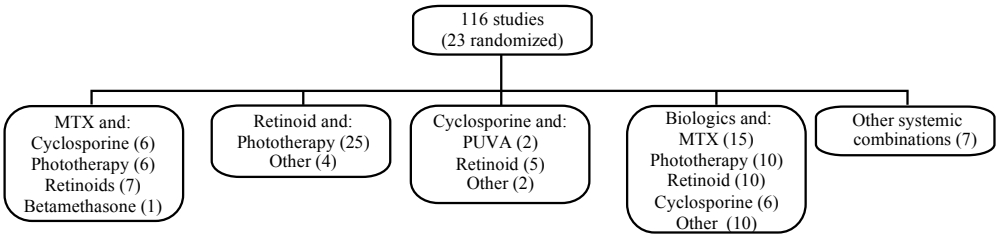

Fig. 1. Number of studies in each of the five main groups. MTX: methotrexate; PUVA: psoralen plus ultraviolet A.

(124 patients) reported on the effect of combining MTX with cyclosporine (3–8). The study by Fraser et al. (3) (Table I) randomized patients with psoriatic arthritis and psoriasis to receive either MTX and placebo or MTX and cyclosporine. The study showed a statistically significant difference between groups on PASI and psoriatic arthritis in favour of combination therapy. In the five remaining uncontrolled studies (Table SII) a beneficial effect of combining MTX with cyclosporine was reported, apart from one case series of four patients published by Korstanje et al. (7). In this report three out of four patients experienced worsening of their psoriasis, which occurred following a dose reduction of cyclosporine due to side effects. In addition, several studies have demonstrated effect and safety of combined treatment with MTX and cyclosporine in patients with rheumatoid arthritis (9, 10).

Six studies examined the effect of combining MTX with phototherapy (125 patients) (11–16). A randomized study by Asawanonda & Nateetongrungsak (11) (Table I) showed a significantly better effect of combined treatment with MTX and NB-UVB compared with NB-UVB monotherapy. Similarly, Shehzad et al. (12) (Table I) demonstrated that patients randomized to MTX and concomitant PUVA therapy achieved clearance earlier than patients treated with either PUVA or MTX monotherapy. All studies, including four non-randomized reports (Table SII), support that an additive effect is achieved when combining MTX and phototherapy, but the long-term risk of skin cancer may be increased and this should be taken into consideration.

MTX was combined with either acitretin or etretinate in seven studies (25 patients) (16–22) (Table SII). No randomized data exist, and the available retrospective data and case reports all show that MTX combined with retinoids led to disease clearance. It is noteworthy that only 25 patients received MTX and retinoid combination treatment, but this is probably due to an increased risk of hepatotoxicity (18).

Gupta & Gupta (23) (Table I) randomly allocated patients to either MTX and per oral betamethasone or MTX monotherapy and found that combination therapy resulted in a longer remission period and shorter time to clearance (no *p*-value provided). This type of combination treatment is not routinely employed.

Combination therapies with retinoids

Twenty-nine studies included retinoids in combination with another systemic treatment. Twenty-six of these studies (1205 patients) examined the effect of combining retinoids with phototherapy (24–49). In the seven randomized studies (Table I) patients were generally allocated to receive either PUVA and placebo or retinoid and PUVA. These controlled data show that the combination of PUVA and retinoid usually achieved disease clearance faster than placebo and PUVA or retinoid monotherapy, and that fewer UVA exposures were needed in the groups that received UVA combined with a retinoid. There seemed to be no difference between etretinate and acitretin regarding efficacy. Ruzicka et al. (30) and Lowe et al. (31) (Table I) randomly allocated patients to receive either acitretin and UVB or placebo and UVB, and also showed that combination therapy with UVB and retinoids had a significantly increased effect on PASI. With regards to type of phototherapy, Özdemir et al. (24) randomized patients to receive either acitretin and PUVA or acitretin and NB-UVB and concluded that both regimens were equally effective. The large number of papers reporting on the retinoid and phototherapy combination reflects the widespread use of this combination. This is in accordance with the general conception that this combination is a safe and effective treatment for moderate-to-severe psoriasis. For the 18 non-randomized studies, see Table SII.

Retinoids were combined in various uncommon ways in three studies (50–52). The study by Ezquerra et al. (50) (Table I) randomized patients to receive either acitretin monotherapy or acitretin and per oral calcitriol and demonstrated a significantly greater PASI reduction in the combination group. Mittal et al. (51) (Table I) randomly assigned patients to either acitretin and placebo or acitretin and pioglitazone (anti-diabetic), and demonstrated a significant difference in PASI reduction in favour of combination therapy. In the randomized trial by Danno & Sugie (52) (Table I) patients were treated with either etretinate and placebo or etretinate and eicosapentaenoic acid (omega-3 fatty acid), and the authors showed a statistically significant difference in favour of combination therapy, with regards to effect and time required to achieve a 50% clearance. None of these treatments are widely employed.

Table I. *Characteristics of the randomized studies (*n = *23)*

Study reference	Study design, No. of patients	Treatment regimen	Results
MTX combinations			
Fraser et al. (3)	Randomized, *n* = 72 Primary endpoint was psoriatic arthritis	(1) MTX (dose not specified) + cyclosporine 2.5 mg/kg/day with dose increase to 4 mg/kg/day over 12 weeks (*n* = 38) (2) MTX (dose not specified) + placebo (*n* = 34)	Reduction in mean PASI from 2 to 0.8 (group 1) and from 2.2 to 1.9 (group 2), $p < 0.001$
Asawanonda & Nateetongrungsak (11)	Randomized, *n* = 24	(1) MTX 15 mg/week + NB-UVB 3 treatments/week from week 4 (mean PASI 18.05, *n* = 11) (2) placebo + NB-UVB 3 treatments/week from week 4 (mean PASI 14.61, *n* = 13) All treatments were discontinued at clearance (90% reduction in baseline PASI) or after 24 weeks of treatment	Group 1: Mean PASI was reduced to 0.31 Group 2: Mean PASI was reduced to 4.62 Difference in PASI score between groups was statistically significant
Shehzad et al. (12)	Randomized, *n* = 60	Group A, *n* = 20, PUVA 4 treatments/week Group B, *n* = 20, MTX 10 mg/week Group C, *n* = 20, MTX 10 mg/week + PUVA 4 treatments/week	Group A: Mean PASI reduction 34.25 to 8.9, mean time of clearance 5.5 weeks Group B: Mean PASI reduction 34.6 to 9, mean time of clearance 8 weeks Group C: Mean PASI reduction 33.75 to 8.5, mean time of clearance 2.5 weeks Difference in mean time of clearance (weeks) between groups was statistically significant
Gupta & Gupta (23)	Randomized, *n* = 40	MTX 15 mg/week + betamethasone 3 mg/week (*n* = 28) or MTX 15 mg/week Patients were treated until the PASI scores were reduced to 95–100% of the baseline values	Combination therapy resulted in a longer remission period of a mean of 91.78 days vs. 20.3 days Time to disease clearance was also less with combination therapy with a mean of 27.13 days vs. 33.09 days Statistically significant findings, *p*-value not provided
Retinoid combinations			
Özdemir et al. (24)	Randomized, *n* = 60	(1) Acitretin 0.3–0.5 mg/kg/day for one week followed by combination with PUVA 3 treatments/week (2) Acitretin 0.3–0.5 mg/kg/day for one week followed by combination with NB-UVB 3 treatments/week Treatment was given for 8 weeks	Both regimens effective with no significant difference in PASI decrease between groups Response rate (PASI 75) was approximately 60% in both groups
Lauharanta & Geiger (25)	Randomized, *n* = 80	(1) Etretinate 50–60 mg/day (*n* = 20) (2) Etretinate 50–60 mg/day for 4 weeks followed by PUVA monotherapy for 6 weeks (*n* = 20) (3) Etretinate 50–60 mg/day for 10 weeks followed by combination therapy with PUVA for 6 weeks (*n* = 20) (4) PUVA alone (*n* = 20) PUVA was given 3 times/week, treatment was given for 10 weeks in all groups	Complete remission at week 10 was observed in 65% of group 3, 25% of group 2, 2% of group 4 and 10% of group 1 ($p < 0.01$) The total UVA doses in group 2 and 3 were significantly lower ($p < 0.001$) than those in group 4
Lauharanta et al. (26)	Randomized, *n* = 34	(1) Acitretin monotherapy 40 mg/day for two weeks, then 20 mg/day + PUVA 3 treatments weekly (*n* = 17) (2) Etretinate monotherapy 40 mg/day for two weeks, then 20 mg/day+ PUVA 3 treatments weekly (*n* = 17)	All patients achieved more than 90% improvement of PASI score in 6–10 weeks No difference in efficacy between groups
Parker et al. (27)	Randomized, *n* = 8	(1) Placebo–PUVA (*n* = 13) (2) Etretinate 0.75 mg/kg/day for 2 weeks than addition of PUVA 3 treatments weekly (*n* = 15)	There were differences between groups regarding disease clearance, total UVA dose needed to clear, number of PUVA exposures to clear or duration of PUVA treatment to clear
Tanew et al. (28)	Randomized, *n* = 60	(1) Acitretin 1 mg/kg/day monotherapy for 5 days then addition of PUVA 4 treatments weekly (*n* = 30) (2) Placebo–PUVA (*n* = 30)	In 7 patients in group 1 and 5 in group 2 treatment was discontinued due to side-effects At least 90% disease clearance was achieved in 22 of 23 patients in group 1 and in 20 of 25 patients in group 2 Both number of UVA exposures (15.3 vs. 21.4) and cumulative UVA dose (58.7 vs. 101.5) were significantly reduced ($p < 0.05$) in group 1 vs. group 2

Table I, *contd.*

Study reference	Study design, No. of patients	Treatment regimen	Results
Saurat et al. (29)	Randomized, $n=58$	(1) Placebo + PUVA 3 treatments/week after 2 weeks of monotherapy (2) Acitretin 50 mg/day + PUVA 3 treatments/week after 2 weeks of monotherapy (3) Etretinate 50 mg/day + PUVA 3 treatments/week after 2 weeks of monotherapy	Duration of treatment until remission: (no *p*-value provided) Group 1: 65.4 days Group 2: 47.8 days Group 3: 57.8 days Number of PUVA exposures until remission: ($p<0.05$) Group 1: 19.9 Group 2: 13.7 Group 3: 16.9
Ruzicka et al. (30)	Randomized, $n=78$	(1) Acitretin 25–35 mg/day + UVB 3–5 treatments weekly ($n=40$) (2) Placebo + UVB ($n=38$)	PASI 75 was achieved in 60% in group 1 vs. 24% in group 2 ($p=0.001$) The median PASI decrease in group 1 was 22 vs. 12 in group 2 ($p=0.0001$)
Lowe et al. (31)	Randomized, $n=34$	(1) Acitretin 50 mg/day + UVB 3 treatments weekly (2) Placebo + UVB	At week 12 mean PASI was less in group 1 vs. group 2 (2.27 vs. 6.36, $p<0.01$)
Ezquerra et al. (50)	Randomized, $n=40$	(1) Acitretin 0.25–0.40 mg/kg/day (2) Acitretin 0.25–0.40 mg/kg/day + oral calcitriol 0.25 µg/day	Difference between baseline and final PASI was 18 in group 2 vs. 13.6 in group 1 ($p<0.05$)
Mittal et al. (51)	Randomized, $n=41$	(1) Acitretin 25 mg/day + placebo (2) Acitretin 25 mg/day + pioglitazone 15 mg/day Treatment administered until patient had disease clearance or for 12 weeks	At 12 weeks reduction in mean PASI was significantly greater in group 2 vs. group 1 (PASI 6 vs. 10, $p=0.04$) No other significant differences
Danno & Sugie (52)	Randomized, $n = 40$	(1) Etretinate 0.3–0.5 mg/kg/day + eicosapentaenoic acid 1800 mg/day (2) Etretinate 0.3–0.5 mg/kg/day + placebo	9 patients in group 1 vs. 3 in group 2 had an excellent clinical response ($p < 0.05$) Duration of treatment required to achieve a 50% reduction in clinical scores was a mean of 5.1 weeks in group 1 vs. 7.6 in group 2 ($p < 0.05$)
Biological combinations			
Zachariae et al. (62)	Randomized, $n = 59$	(1) Etanercept + MTX 7.5–25 mg/week tapered and discontinued at week 4 ($n = 28$) (2) Combination therapy throughout the study ($n = 31$)	PASI 75 at both 12 weeks (28% vs 55%) and 24 weeks (32% vs 70%) was significantly better for combination therapy
Mease et al. (63)	Randomized, $n = 185$ Primary endpoint was psoriatic arthritis	(1) Alefacept + MTX 10–25 mg/week ($n = 123$) (2) Placebo + MTX 10–25 mg/week ($n = 162$) Some patients received additional prednisolone 10 mg/day	PASI 50 response 53% in combination group vs. 17% in placebo group ($p < 0.001$)
Gisondi et al. (77)	Randomized, $n = 60$	(1) Acitretin 0.4 mg/kg/day ($n = 20$) (2) Etanercept ($n = 22$) (3) Etanercept + acitretin 0.4 mg/kg/day ($n = 18$)	Achievement of PASI 75 at week 24: Group 1: 6 patients, group 2: 10 patients and group 3: 8 patients, $p = 0.001$ (etanercept groups vs. acitretin alone) Mean BSA improvement at week 24: Group 1: 46%; group 2: 80%; group 3: 78%, $p = 0.03$
Jacobe et al. (81)	Randomized, $n = 16$ 1 patient in placebo group excluded because of non-compliance	(1) Alefacept + NB-UVB 3 treatments/week (2) Placebo + NB-UVB 3 treatments/week Twelve week trial period	No significant difference in PASI reduction was observed
Legat et al. (82)	Randomized half body comparison, $n = 14$	Alefacept + NB-UVB 3 treatments/week until PASI 3 or lower	After 12 weeks of treatment the mean PASIs on UV-irradiated and non-irradiated body halves were significantly reduced by 81% and 62% respectively, $p < 0.001$ At week 12 a PASI 75 response had been achieved more often on UV-irradiated body halves (86%) than on non-irradiated body halves (43%)

Table I, *contd.*

Study reference	Study design, No. of patients	Treatment regimen	Results
Ortonne et al. (83)	Randomized, $n = 60$	(1) Etanercept (2) Etanercept + UVB treatment for 6 weeks (3) Etanercept + UVB treatment for 12 weeks At one centre UVB was narrowband (NB), at the other centre UVB was broadband (BB)	Centre 1: after 4 weeks of treatment PASI 50 was achieved in 44% of patients receiving monotherapy vs. 90% (6 weeks NB-UVB) and 82% (12 weeks NB-UVB) Centre 2: after 4 weeks of treatment no patient receiving monotherapy reached PASI 50 In the combination groups 22% receiving 6 weeks BB-UVB and 22% receiving 12 weeks BB-UVB reached PASI 50 after 4 weeks
Other systemic combinations			
Reitamo et al. (98)	Randomized, multicentre, $n = 150$	Rapamycin monotherapy or combined with low-dose cyclosporine 1.25 mg/kg/day vs. cyclosporine monotherapy 5 mg/kg/day	Combination treatment resulted in PASI reduction of 63.7% Cyclosporine monotherapy resulted in PASI reduction of 70.5% No significant difference between groups Rapamycin monotherapy was not effective
Merk et al. (102)	Randomized, $n = 52$	(1) Cimetidine 400 mg × 3/day + chlorpheniramine 4 mg × 3/day (2) Placebo + chlorpheniramine 4 mg × 3/day (3) Cimetidine 400 mg × 3/day + placebo (4) Placebo + placebo	No effect on psoriasis of any treatment regimen

UVB: ultraviolet B; MTX: methotrexate; NB-UVB: narrowband UVB

Combination therapies with cyclosporine

Nine non-randomized studies investigated the effect of systemic combination therapy involving cyclosporine (Table SII). Two small prospective studies (42, 53) (21 patients) reported on the combination of cyclosporine and PUVA. The scarcity of reports probably reflects the fact that this combination is seldom used and considered contraindicated due to the increased risk of squamous cell carcinoma, which has also been shown by Marcil & Stern (54).

Cyclosporine was combined with retinoids in five papers (55–59) (14 patients) and in three studies ($n = 6$) combination treatment was effective. Both cyclosporine and retinoids may increase cholesterol and triglyceride levels, which mandates strict monitoring of lipids when used in combination.

Two prospective studies (60, 61) (17 patients) combined cyclosporine with either mycophenolate mofetil or hydroxyurea and showed an overall good effect on PASI.

Combination therapies using biologics

Biologics were combined with another systemic drug in 51 studies. In 15 of these, a biological agent was given with MTX (385 patients) (62–76). Zachariae et al. (62) (Table I) randomized 59 patients, who had an inadequate response to MTX treatment, to receive either etanercept and MTX tapered or combination therapy throughout the whole study period of 24 weeks. It was shown that significantly more patients in the combination group achieved PASI 75 than patients who had MTX tapered. Not surprisingly, the study by Mease et al. (63) (Table I) in which patients were randomized to either alefacept and MTX or MTX and placebo also showed that alefacept and MTX was superior to MTX alone in improving both psoriasis and psoriatic arthritis. For the remaining 13 non-randomized studies, see Table SII.

Biologics were combined with retinoids in 10 studies (137 patients) (21, 21, 68, 69, 70, 73, 77–80). In the randomized work by Gisondi et al. (77) (Table I) treatment was given either as etanercept monotherapy, acitretin monotherapy or etanercept and acitretin combination therapy. It was demonstrated that more patients receiving etanercept either alone or combined with acitretin achieved PASI 75 than patients on acitretin monotherapy. There was no difference in efficacy between etanercept monotherapy and etanercept in combination with acitretin. For non-randomized data (nine studies), see Table SII.

Ten studies (271 patients) evaluated the effect of combing biological treatment with phototherapy (70, 81–89). Jacobe et al. (81) (Table I) randomized patients to either alefacept and NB-UVB or placebo and NB-UVB with no significant difference in PASI reduction. In

the paper by Legat et al. (82) (Table I), patients treated with alefacept were irradiated with NB-UVB on one half of the body, which resulted in a significant effect on PASI and time to clearance on the irradiated side. Ortonne et al. (83) (Table I) conducted a randomized study in which patients were treated with either etanercept monotherapy or etanercept and phototherapy. They showed that combination therapy resulted in a significantly higher number of patients with a PASI 50 after 4 weeks of treatment. For data from the seven non-randomized studies, see Table SII.

A biological agent was combined with cyclosporine in six non-randomized studies and case reports (67, 69, 70, 90–92) (88 patients, Table SII), and overall this combination proved effective.

Ten retrospective studies and case reports (67, 72, 73, 76, 78, 93–97) (Table SII) described a total of 36 patients treated with biologics in combination with other systemic agents such as prednisolone, MTX and prednisolone, azathioprine, acitretin, acitretin and prednisolone, hydroxyurea, MTX and cyclosporine or another biological agent. All studies reported that combination therapy was effective.

Biological combinations, especially anti-tumour necrosis factor (TNF)-α with MTX, prednisolone and azathioprine are commonly used and considered safe and effective combinations in rheumatology and gastroenterology.

Other systemic combination therapies

Seven papers investigated the effect of other uncommon non-biological combinations (32, 98–103). The randomized multicentre study by Reitamo et al. (98) (Table I) examined the effect of rapamycin monotherapy vs. rapamycin and cyclosporine and found no difference in PASI reduction between the two groups after 8 weeks. Merk et al. (102) (Table I) randomized patients to receive either cimetidine and chlorpheniramine, placebo and chlorpheniramine, cimetidine and placebo, or placebo, and found all regimens ineffective. For the remaining five non-randomized papers, see Table SII.

DISCUSSION

Patients with moderate-to-severe psoriasis often depend upon systemic combination therapy for varying time periods to achieve and sustain disease remission. The advantages of combination therapy are, first and foremost, the ability to reduce dosages of the individual agents to reduce side effects, while at the same time achieving an additive or synergistic effect. Numerous possibilities for combination therapies exist, but very few are supported by controlled data from controlled clinical trials as only 23 of 116 identified studies were randomized. The majority of the randomized (and uncontrolled) studies reported on the combination of retinoids and phototherapy, which is generally considered safe and effective, as it is the only thoroughly investigated combination and one of the most widely used. Some combination regimens are considered contraindicated and include PUVA and cyclosporine and PUVA and MTX. The risk of squamous cell carcinoma is increased by cyclosporine in previously PUVA exposed patients (54) and in patients treated with PUVA and high-dose MTX (104). In contrast, the risk of squamous cell carcinoma may be reduced by the combination of PUVA and retinoid (105). Combining MTX with a retinoid is not considered absolutely contraindicated, but should be administered with caution, as life-threatening hepatotoxicity has been reported in patients receiving this combination (18).

Regarding the newer biological agents, the combination of anti-TNFα and MTX has been thoroughly investigated, especially for the treatment of rheumatoid arthritis. At present, only a few studies have examined the effect on psoriasis of combining biologics with other systemic therapies. However, treatment with a combination of two biological agents should probably be restricted until further data on long-term side effects are available. Biological agents are not known to cause nephrotoxicity, hepatotoxicity or bone marrow suppression, and therefore it is possible that they can be combined without side effects. However, since additive immunosuppression might be induced if a biological agent is combined with another immunosuppressant, such as cyclosporine, safety issues remain until more data are available.

The need for combination therapy in patients with moderate-to-severe psoriasis is obvious, and combined treatment with retinoid and phototherapy is the only well-documented combination regimen for this disease. Severe cases, however, may warrant the use of short-term combination therapy with a biological agent and phototherapy or a cytostatic in order to achieve remission, followed by maintenance therapy with biological monotherapy.

Further controlled research is required to identify the safest and most effective combinations.

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