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Combination therapies in psoriasis

Psoriasiste kombinasyon tedavileri

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Abstract

Topical corticosteroids and vitamin D analogs can be combined with other topical, systemic, and biological agents. The effect of methotrexate can be enhanced with ultraviolet B (UVB) or psoralen ultraviolet A (PUVA). When a biological agent remains insufficient, the first agent to be added to the treatment is methotrexate. The use of acitretin in combination with phototherapy (both UVB and PUVA) has a synergistic effect. A UVB therapy may be combined with topical tar and anthralin as well as with etanercept and adalimumab, which are anti-tumor necrosis factor-α therapies.
Keywords: Psoriasis, combination therapies, UVB, biologics

Öz

Topikal kortikosteroidler ve vitamin D analogları; diğer topikal tedavilerle, sistemik tedavilerle ve biyolojik ajanlarla kombine edilebilir. Metotreksatın etkisi ultraviyole B (UVB) veya psoralen ultraviyole A (PUVA) ile artırılabilir. Biyolojik ajan yetersiz kaldığında tedaviye eklenebilecek ilk sıradaki ajan metotreksattır. Asitretinin fototerapi ile (hem UVB, hem PUVA) ile birlikte kullanımı sinerjistik etkiye sahiptir. UVB tedavisi, topikal katran ve antralinle ile ve anti-tümör nekroz faktörü-α tedavilerden etanersept ve adalimumab ile kombine edilebilir.
Anahtar Kelimeler: Psoriasis, kombinasyon tedavisi, UVB, biyolojikler

Topical therapies

Topical corticosteroids and vitamin D analogues can simply and reliably be combined with other topical therapies as well as with systemic and biological agents.

Methotrexate

The effect of methotrexate can be enhanced with ultraviolet B (UVB) or psoralen ultraviolet A (PUVA). However, long-term outcomes inevitably involve increased phototoxicity. Phototoxicity was seen in PUVA but not in UVB[1]. In refractory psoriasis, cyclosporine may be added to methotrexate for a short period of time. Side effects such as hepatotoxicity and nephrotoxicity can be controlled more easily with lower doses[2]. When a biological agent proves insufficient and addition of a systemic agent to the treatment is needed, then the agent to be considered first should be methotrexate. This is because methotrexate is the most suitable agent to be combined with a biological therapy as it also reduces immunogenicity[2].

Cyclosporine

Cyclosporine may be combined with topical corticosteroids, anthralin and vitamin D analogues[2]. Due to its immunosuppressive effect, cyclosporine is used more at the washout stage of a rotational and consecutive therapy rather than in combinations. A phototherapy and cyclosporine combination is contraindicated. Its combination with acitretin may be used at the transition phase of a consecutive therapy. Its combination with methotrexate leads to an increase in the immunosuppressive effect. Its combination with biological agents is also not recommended.

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Retinoids

Use of acitretin in combination with phototherapy (both UVB and PUVA) has a synergistic effect[3]. Acitretin may be combined with etanercept[1].
Phototherapy: combining phototherapy with a topical therapy may be appropriate. An UVB therapy may be combined with topical tar and anthralin. They will improve the inadequacy of UVB to penetrate thick plaques[4]. Narrow-band UVB (nbUVB) therapy has been used in combination with anti-tumour necrosis factor (anti-TNF-α) medications etanercept and adalimumab, and found effective[5,6].

Biological agents

All parameters monitored for biological agents used as a monotherapy should also be monitored for any combination with conventional systemic therapies. As a practical guidance, the frequency of follow-ups should be specified with reference to the follow-up frequency of the drug that requires the most strict monitoring. When a synergistic toxicity is expected, follow-up intervals may be shortened and addition of some other parameters may be needed. One of the conventional systemic medications (methotrexate, acitretin) may be added to the biological therapy to increase the efficacy of a monotherapy with a biologic, to secure an optimal risk-benefit profile, to decrease the risk of immunogenecity, or to engage in a long-term disease management. The conventional systemic medication should be added starting from the lowest recommended dose, for example, methotrexate 5-10 mg/week. A combination with cyclosporine is not appropriate due to safety concerns. A transition to another biological drug may be considered[7].
The combinations of etanercept with methotrexate and etanercept with acitretin are suitable combinations to increase efficacy without extra toxicity[8,9]. There is no study on the combined use of infliximab and methotrexate. However, some studies argue that addition of methotrexate in low doses, i.e. 7.5 mg/week prevents any loss of efficacy by suppressing infliximab's neutralizing antibody formation and enables the continuation of the efficacy.
A combination of adalimumab with methotrexate also improves efficacy by reducing immunogenecity[10]. A combination of ustekinumab with methotrexate is anecdotally known to increase efficacy, particularly in psoriatic arthritis. A combination of an anti-TNF agent with phototherapy is unfavourable as it will increase phototoxicity[10]. There are studies, however, arguing that a combination of etanercept with nbUVB or adalimumab with nbUVB would increase the efficacy[5,6]. If the response to a TNF antagonist is insufficient, a switch to another TNF antagonist can be made and methotrexate may be added to the new agent to prevent antibody development or a switch to ustekinumab can be made[3].
Treatment with ustekinumab will involve the same procedure as that of an anti-TNF therapy. In combination therapies, topical agents may be added to methotrexate. Table 1 summarizes evidence-based literature data on combination therapies used in psoriasis[11]. Literature on combinations with IL-17 and IL-23 inhibitors is not sufficient, but there seems to be no safety concerns[12]. Study registries show that most of the patients receiving combination therapies are those who have accompanying PsA, but we should keep in mind that safety-related events are more common in combination therapies than in monotherapies[12,13].

Rotational treatments

Rotational administration of systemic therapies and phototherapy is recommended to reduce cumulative toxicity and shorten the length of treatment. Rotational cyclosporine and methotrexate therapies are recommended to reduce side effects. In low doses, both hepatotoxicity and nephrotoxicity will have been prevented. However, since cyclosporine may increase photocarcinogenicity after phototherapy, it is not recommended. When treating psoriasis, it is always possible to switch from standard therapies to biologics, from a biologic to another biologic or from a biologic therapy to a standard therapy. When switching between biological therapies, the new biological agent may be introduced at the scheduled time of administering the next dose of the agent being used.

Suggestions for switching from a conventional systemic therapy to a biological therapy

When a therapy change is to be made for safety reasons, a run-in period may be needed until the safety parameters return to normal. When replacing a therapy due to inefficacy, a direct change of the therapy or a transition to a period where two therapies are administered at the same time may be considered. A transition from acitretin to a TNF antagonist or ustekinumab may be made without any washout period or through a period where the two therapies are used at the same time. However, for having used acitretin, contraception should continue for a period of 3 years. A transition from cyclosporine to biologics may be made without a washout period. In such a transition from cyclosporine to biologics, a short period, between 2 and 8 weeks, of concurrent use may be considered to reduce the risk of rebound. This period should be kept at a minimum and the cyclosporine dose should be decreased as fast as possible. A transition

Table 1. Combination therapies in psoriasis*

	Cyclosporine	Methotrexate	Retinoids	Adalimumab	Etanercept	Infliximab	Ustekinumab	UVB	PUVA
Cyclosporine		+	+	-	-	-	-	-	-
Methotrexate	+		+	+	+	+	+	+	+
Retinoids	+	+		(+)	+	(+)	?	+	+
Adalimumab	-	+	(+)		?	?	-	+	-
Etanercept	-	+	+	?		?	-	+	-
Infliximab	-	+	(+)	?	?		-	?	-
Ustekinumab	-	+	?	-	-	-		?	?
UVB	-	+	+	+	+	?	?		+
PUVA	-	+	+	-	-	-	?	+	

+: Beneficial, ?: No evidence (+)/(-): Beneficial or not based on case reports, -: Not recommended, UVB: Ultraviolet B, PUVA: Psoralen ultraviolet A, *Adapted from Domm and Mrowietz[11] (2011)

from methotrexate to biologics may be made without a washout period. Methotrexate may concurrently be used with biologics[7].

Suggestions for switching between biological therapies

In cases where a transition between biological agents is decided due to inefficacy, it is recommended to make the transition at the time of the next scheduled dose without a washout period and by following the maintenance dose after the standard induction dose. Studies have also tried transitions with other agents in their maintenance doses and found no loss of efficacy. In a transition due to inefficacy, a weaker response to the new agent than expected may occur. In transitions due to inefficacy, it seems more appropriate to switch to a different class. However, if the transition is due to a decreasing efficacy, it is possible to choose a different agent within the same class. Data on transitions from IL-15 inhibitors to IL-23 inhibitors is limited; there are real world experiences data showing that a transition from an IL-17 inhibitor to an anti-TNF or ustekinumab is effective[14].

Safety issues associated with biological agents may be universal, or specific to the drug or drug class. For example, while safety issues specific to the anti-TNF class are tuberculosis, congestive heart failure, multiple sclerosis and lupus erythematosus, those associated with IL-17A inhibitors are candidiasis and inflammatory bowel diseases. In case lupus develops due to anti-TNF agents or IL-17 inhibitors, a transition to ustekinumab may be preferred and if it develops due to an anti-TNF agent, a transition to a different agent in the same class may be considered[15,16]. Since developing a paradoxical reaction is believed to be a class effect, it is recommended to choose a different target molecule when making a transition due to a paradoxical reaction. Alopecia areate, however, is agreed to be a drug specific side effect; thus it may not develop with a different agent in the same class[14].

If a transition is necessary for safety reasons, a drug-free period may be needed until the safety parameters return to normal or become stable. When switching from adalimumab to other biological agents, the new drug may be given at the time of the next scheduled dose of adalimumab (typically after 2 weeks). When switching from etanercept to other agents, the new drug may be given at the time of the next scheduled dose of etanercept (typically after 1 week). A transition from infliximab to other agents, especially due to inefficacy, may be made as early as possible, 2-4 weeks after the last injliximab dose. A transition from ustekinumab to other agents should be made after 8-12 weeks. However, in the case of a treatment failure, starting it as early as possible, in 2-4 weeks, may be considered[7].

Suggestions for suspension or termination of a biological therapy

Suspension of a biological therapy is generally not recommended. In patients with moderate to severe psoriasis, suspending the biological therapy is quite difficult without taking the risk of disease relapse or the risk of efficacy decline in the resumed treatment. It is recommended to administer a biological therapy using a continuous treatment protocol, without any breaks. However, if cleansing has been accomplished along with good quality of life outcomes that are maintained for a long time, for example for a year as a minimum, discontinuation of the biological therapy may be considered with careful monitoring and in agreement with the patient. Upon patient request, the therapy may be discontinued in patients who previously had a disease-free period or who have a stable plaque psoriasis, who do not have an apparent comorbidity, and who did not experience any worsening of their disease during a quality of life-impairing disease, previous dose decreases or interruptions between treatments. However, since biological agents are preferred mostly in patients with moderate to severe psoriasis and are used after lack of response to systemic treatments, patients using biological agents usually do not meet the above criteria. Additionally, treatment options for these patients are limited at the time of restarting the treatment after a period of non-response[7].

Intermittent treatment may involve the risk of developing antibodies against biologics. This is especially true when a biological agent in the form of monoclonal antibody is used as a monotherapy. Intermittent treatment has also been observed to increase the risk of injection and infusion reactions.

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