Fotoquimioterapia e Fototerapia Ultravioleta B de Banda Estreita como Resgate de Terapêutica Biológica em Falência Secundária: Um Estudo Coorte Retrospetivo

Duarte B[1], Serrão V[1], Rocha Páris F[1], Marques Pinto G[1], Apetato M[2], Cabete J[1]
[1]Department of Dermatology, Hospital de Santo António dos Capuchos – Centro Hospitalar de Lisboa Central, Lisbon, Portugal
[2]Department of Dermatology, Hospital de Cascais Dr. José de Almeida, Cascais, Portugal

RESUMO – **Introdução**: A sobrevida dos biológicos no tratamento da psoríase é sobretudo limitada pela perda de efetividade ao longo do tempo. Estratégias que permitam prolongar a retenção terapêutica são necessárias. O objetivo foi estudar a efetividade e tolerabilidade da fototerapia ultravioleta B de banda estreita e da fotoquimioterapia (terapia PUVA) para resgatar a resposta do fármaco biotecnológico em falência secundária. **Métodos**: Estudo coorte retrospetivo de 18 doentes adultos com psoríase em placas moderada a grave sob biológico que receberam tratamento adjuvante com fototerapia após perda secundária de eficácia **Resultados**: Doze doentes realizaram PUVA adjuvante com etanercept e adalimumab em 13 e 5 ciclos de tratamento, respetivamente. Foi observada resposta clínica em 72,2% dos ciclos (PASI75 55,5%). Verificou-se uma redução do PASI mediano em 73% e uma resposta sustentada ao biológico de 25 meses (mediana) após término da fototerapia. Um melanoma foi diagnosticado no *follow-up*. Seis doentes realizaram fototerapia ultravioleta B de banda estreita adjuvante ao etanercept, adalimumab e ustecinumab em 7,3 e 2 ciclos terapêuticos, respetivamente. Uma resposta completa foi observada em 75% dos ciclos (PASI75 41,7%). Verificou-se uma redução do PASI mediano em 80% e uma resposta sustentada ao biológico após término de foto de 21 meses (mediana). **Conclusão**: Este estudo demonstra a experiência favorável de um centro terciário no uso de terapia PUVA e fototerapia ultravioleta B de banda estreita para resgatar a resposta e prolongar a retenção dos biológicos no tratamento da psoríase. Estudos prospetivos são necessários para substanciar esta interessante estratégia na atual era de fármacos biológicos.
PALAVRAS-CHAVE – Fármacos Fotossensibilizantes; Fotoquimioterapia; Psoríase; Terapia PUVA.

Can Psoralen Ultraviolet-A or Narrowband Ultraviolet-B Salvage the Biologic Drug Response After a Secondary Failure? A Retrospective Cohort Study

ABSTRACT – ***Introduction:*** *Biologic drug survival in psoriasis is mainly limited by a decrease of effectiveness over time. Strategies to improve retention rates are needed. Our purpose was to evaluate the efficacy and tolerability of concurrent narrowband ultraviolet-B (NB-UVB) or photochemotherapy (PUVA) to salvage the biologic drug in secondary non-response.* ***Methods:*** *Retrospective cohort study of 18 adults with moderate-to-severe plaque psoriasis treated with biologics who received concurrent phototherapy after a secondary efficacy loss.* ***Results:*** *Twelve patients underwent PUVA concurrently with etanercept and adalimumab in 13 and 5 cycles, respectively. Clinical response was observed in 72.2% of cycles (PASI75 55.5%). Median PASI decreased by 73%. Sustained response was observed for 25 months (median). A malignant melanoma was identified during follow-up. Six patients underwent NB-UVB concurrently with etanercept, adalimumab and ustekinumab in 7.3 and 2 cycles, respectively. Clinical response*

Correspondência: Bruno Duarte
Department of Dermatology - Hospital de Santo António dos Capuchos
Centro Hospitalar de Lisboa Central
Alameda Santo António dos Capuchos
1169-050, Lisbon, Portugal
E-mail: brunoduarte@campus.ul.pt
DOI: https://dx.doi.org/10.29021/spdv.77.1.1004

Recebido/*Received*
07 Novembro/*November* 2018
Aceite/*Accepted*
21 Janeiro/*January* 2019

Artigo Original

was observed in 75% of cycles (PASI75 41.7%). Median PASI decreased by 80%. Sustained responde was observed for 21 months (median). ***Conclusions:*** *This study adds real-life evidence that PUVA and NB-UVB are effective options to salvage and improve the long-term performance of biologic drugs. Further efficacy and safety data, especially addressing the skin malignancy risk, should be sought to clarify the role of this interesting approach in the modern era of improved biologic therapies.*
KEYWORDS *– Photochemotherapy; Photosensitizing Agents; Psoriasis; PUVA Therapy.*

INTRODUCTION

The introduction of biologics was a revolutionary achievement in the psoriasis therapeutic armamentarium. Countless recalcitrant cases were finally managed and significant improvements in patients' quality of life naturally followed.[1] Nevertheless, with increasing experience derived from large disease-based registries,[2,3] it becomes evident that biologics have a limited survival, making it predictable that either increasing the dose or switching to another drug, with costly induction phases, will eventually be necessary. In this context, strategies to salvage the response to the biologic drug in the event of a loss of efficacy would be welcome.

Combining, at least transiently, the biologic with a conventional systemic treatment is an attractive and interesting strategy. Indeed, both efficacy and drug survival appear to improve when combined with metrothrexate[3,4] but the latter end-organ toxicity and potential hazards of a dual immunomodulator regimen might limit its use in some patients. Phototherapy is a time-honored treatment modality for psoriasis which has the potential advantage of causing less disruption on the systemic immunological axis, when compared to oral or injectable immunomodulators. In a limited number of trials, narrowband ultraviolet-B (NB-UVB) has shown to improve the biologic drug response,[5,6] and even to recover it after secondary failure.[4] On the other hand, no studies to date have assessed the efficacy and tolerability of psoralen ultraviolet-A (PUVA) for this purpose. This study aims to assess the efficacy and tolerability of phototherapy, both PUVA and NB-UVB, to restore the clinical response to a biologic drug.

METHODS

A retrospective cohort study was performed. Data was captured by scrutinizing the written and electronic medical records of the Dermatology Psoriasis and Phototherapy Units of a large tertiary hospital. Patients were considered eligible if they were aged 18 years or older, followed at this tertiary dermatology department between January 2000 and June 2017, and met the following criteria:

1. Moderate-to-severe plaque-type psoriasis [failure of at least of one conventional systemic treatment plus, at least, one of the following criteria: Psoriasis Area Severity Index (PASI) > 10, Body Surface Area > 10%, Dermatology Life Quality Index > 10, lesions on sensitive areas], with a confirmed diagnosis by at least two dermatologists, treated with a biologic drug (etanercept, infliximab, adalimumab, ustekinumab) with a good-to-excellent primary response but secondary loss of response (PASI 75 as initial response and < PASI 50 during maintenance therapy, respectively). Standard licensed dosing regimens were used.

2. Phototherapy (PUVA with 2x/week UVA irradiation after oral ingestion of 0.6 mg/kg of 8-MOP or NB-UVB 3x/week) was prescribed to salvage the biologic therapy response, without withdrawing the biologic drug or changing the dosing regimen. Standard irradiation doses were applied and selected by a trained physician according to the patient's Fitzpatrick skin type.

Clinical response was defined as the achievement of PASI 50 plus at least a 3-month sustained response after the last phototherapy treatment. The clinical response was further subclassified into partial (PASI 50-75) or complete (PASI 75). All patients must have had, at least, a 1-year follow-up. Concomitant antipsoriatic drugs at the beginning of the phototherapy, other than the biologic drug, were continued without dose or schedule modifications.

RESULTS

A total of 18 patients (11 women and 9 men) were eligible for the analysis. Mean age was 48 years (31-71) and the mean evolution of the disease was 21 years. All patients had plaque type psoriasis, 5 with additional arthropathic involvement. The median number of past conventional treatments was 3 (2-7). The median number of biologic drug switches was 1. Nine patients (50%) had undergone phototherapy before, of which 4 (45%) were responders. All patients in the enrolled group had an acceptable compliance to the phototherapy regimen (defined as <3 treatments missed in any 4-week period) (Table 1).

Altogether, a total of 31 combination cycles were analyzed individually and according to the employed phototherapy modality. Combination treatment distribution per year of completion is illustrated on Fig. 1. Six patients were treated with combination therapy for more than one occasion/cycle.

Table 1 - Patient's general characteristics.

Number of patients, n (male/female)	18 (9/11)
Age – mean (range)	48 (31-71)
Diagnosis, n (%)	
• Chronic plaque psoriasis	48 (31-71)
• Concomitant arthropathic involvement	48 (31-71)
Evolution of psoriasis (years) Median (range)	21 (7-28)
Past conventional treatments: mean (range)	3 (2-7)
Number of biologic drug switches (median)	1
Past phototherapy, n (%)	9 (50%)
Responders, n (%)	4 (45%)

The study results and other observations are summarized in Table 2 and Fig.s 2 and 3.

Twelve patients underwent PUVA therapy (18 combination cycles, mean of 1.5 cycles per patient). The biologic drugs were, per combination cycle, as follows: etanercept in 13 cycles and adalimumab in 5 cycles. Other concomitant antipsoriatic drugs included fixed combination calcipotriol/betamethasone gel (once daily) in all treatment cycles, methotrexate (10-22.5 mg/week) was associated in 25% and acitretin (10-25 mg/thrice weekly) in 16.7%. The mean number of phototherapy sessions on each cycle was 21.8 (16-57), with a mean cumulative UVA dose of 148.9 J/cm^2 (97-225). A clinical response was achieved in 72.2% of the cycles (PASI 90-100 33.3%, PASI 75-90 22.2%, PASI 50-75 16.7%). Median initial and final PASI was, respectively, 7.4 and 2 (73% decrease). After PUVA cessation, a sustained response to the biologic therapy was observed for a median of 25 months (4-95). In the non-responders' group (27.8%), a switch to another biologic was performed in 3 cases, while in the remaining 2 cases the drug was maintained, but other therapeutic associations were explored.

The following side effects directly attributed to PUVA were: therapeutic photo-aggravation (1 case), abdominal discomfort (1 case) and phototherapy-induced erythema (PIE, 3 cases).

As possibly-related side effects, we identified a malignant melanoma *in situ* in a heavily immunosuppressed 71-year-old, skin type II female patient which had been developing multiple atypical nevi for the past 2 years. She had a severe and debilitating case of psoriatic arthritis, for which she was being treated concomitantly with adalimumab, phototherapy (accumulated lifetime dose of 718 J/cm^2) and methotrexate 22.5 mg weekly. Eighteen years before, she had been treated with cyclosporine only for three months. No other risk factors for melanoma were identified.

Six patients underwent NB-UVB (12 combination cycles, mean of 2 cycles per patient). The biologic drugs were, per combination cycle, as follows: etanercept in 7 cycles, adalimumab in 3 cycles and ustekinumab in 2 cycles. Other concomitant antipsoriatic drugs included fixed combination of calcipotriol/betamethasone gel (once daily) in all treatment cycles, methotrexate (10-15 mg/week) in 33.3%. The mean number of phototherapy sessions received on each therapeutic cycle was 32.25 (19-52), with a mean UVB cumulative dose of 46.28 J/cm^2 (23.3-81.1). A clinical response was achieved in 75% of cases (PASI 90-100 33.3%, PASI 75-90 8.4%, PASI 50-75 33.3%). Median initial and final PASI were, respectively, 5 and 1 (80% decrease). After NB-UVB cessation, a sustained response to the biologic drug was observed for a median of 21 months (9-48). In the non-responders' group (25%), a switch to another biologic was performed in 1 case, while in the remaining 2 cases the drug was maintained, but other therapeutic associations were explored.

As adverse effects, a single case of PIE was observed. Another patient, a 46-year-old, skin type II man developed multiple atypical nevi. No skin cancers or other adverse events were observed during follow-up.

Table 2 - Characterization of the phototherapy treatments in the different groups of phototherapy (PUVA and NB-UVB), drugs used concomitantly, including biologics that were associated with secondary failure, and side effects of combined therapies.

Biologic drug/phototherapy characteristics	PUVA group	NB-UVB group
Combination therapy cycles evaluated	18	12
• Cycles per patient (median)	1.5	2
Median follow-up (months)	67	50.5
Biologic drug		
• Etanercept	72.2%	67.7%
• Adalimumab	27.8%	27.3%
• Ustekinumab	0%	5%
Concomitant antipsoriatic drugs		
• Calcipotriol/betamethasone gel	100%	100%
• Methotrexate	25%	33.3%
• Acitretin	16.7%	0%
Reason for combination therapy		
• Loss of efficacy	9	5
• Transient exacerbation	9	7
Phototherapy treatments, mean per patient (range)	21.8 (16-57)	32.25 (19-52)
Cumulative dose, mean per patient (range)	148.9 (97-225)	46.28 (23.3-81.1)
PUVA-biologic drug therapy direct side effects		
• Phototherapy-induced erythema	3	1
• Therapeutic photo-aggravation	1	0
• Abdominal discomfort	1	0
Remarkable findings during follow-up		
• Malignant melanoma	1	0
• Multiple atypical nevi	1	0

Artigo Original

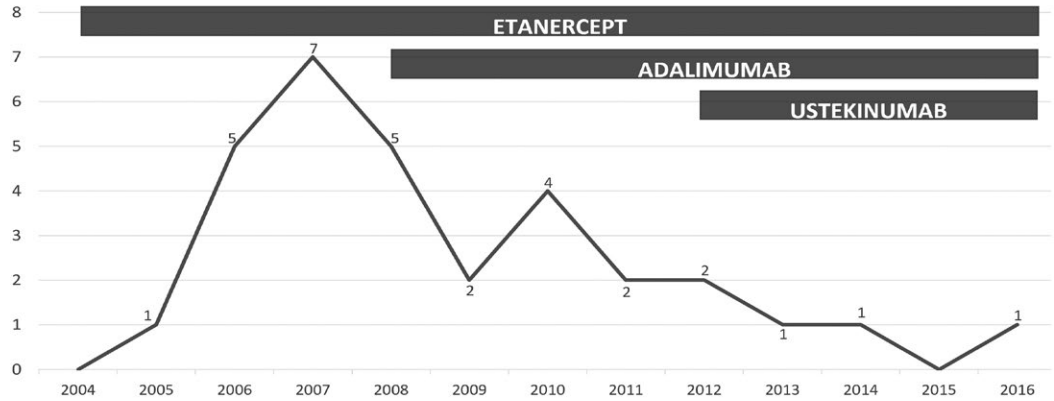
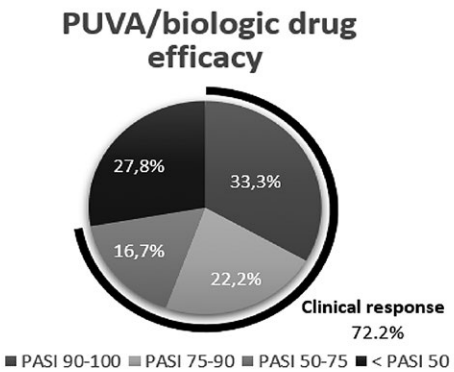


Figure 1 - Number of patients that underwent phototherapy, by year, to salvage the biologic drug response in the Phototherapy Unit of a Tertiary Hospital (18 patients, 31 cycles). Shortage of further effective biologics made this strategy a valuable option in the pre-2008 era.



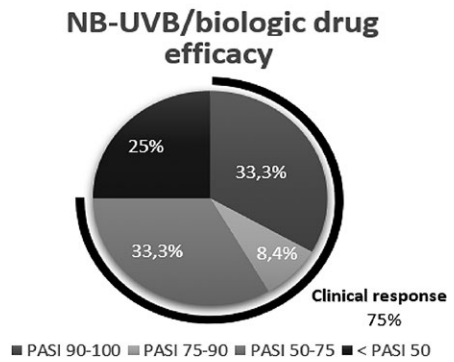


Figure 2 and 3 - Efficacy of PUVA and NB-UVB, respectively, in salvaging the biologic drug response.

DISCUSSION

Despite the evidence gap and absence of decision-making guidelines, a recent large European multinational study demonstrated that 9.9% of biologic treatments were combined with conventional systemic therapies, of which NB-UVB was the second most frequent option (25%), albeit largely surpassed by methotrexate (72.9%).[7] Effectively, success of NB-UVB as adjunct therapy to etanercept,[6,8-13] adalimumab,[5,14] and ustekinumab[15] has been reported before. Photochemotherapy, on the other hand, is very rarely used in combination treatment strategies (<0.1%),[7] which is in line with the paucity in the literature. Nevertheless, it has its own advantages. As monotherapy, it is regarded as more efficacious, requiring fewer treatments for clearance and sustained longer remission rates[16] than NB-UVB. Long-term safety concerns have yet limited its use. Currently, PUVA has a relative contraindication regarding combination strategies with tumor necrosis factor alfa (TNF-α) antagonists.[17]

With our study, we add real-life evidence that phototherapy can improve the long-term therapeutic performance of biologic drugs, by restoring a durable response in the event of an efficacy loss: with PUVA and NB-UVB, respectively, PASI 50 was achieved in 72.2% and 75% of the cycles, and PASI 75 was achieved in 50% and 41.4% of the cycles. Furthermore, to the best of our knowledge, we present the first study assessing the combination treatment potential of biologics with PUVA. As observed in Fig. 1, phototherapy was mostly employed in our center as an adjunct modality to biologics before 2008, explaining the overrepresentation of etanercept in our study. In this period dermatologists were deprived of the wide repertoire of targeted therapies available nowadays, therefore secondary failure in severe psoriasis patients was frequent and often a challenging and disappointing task. As we demonstrated, phototherapy was a rewarding effort in these times to increase the biologic drug retention rates. Although less used in current practice due to the increasing number of biologics available, combining these drugs with phototherapy should still be considered as an interesting strategy for selected cases. For example, a cutaneous flare in an arthropathic psoriasis patient treated with an anti-TNF therapy will probably benefit more from a skin-directed approach such as phototherapy, before trying a biologic swap which might destabilize the otherwise well-controlled joint involvement. In our perspective, phototherapy should still be considered a useful tool to recover the response of a biologic drug in secondary failure, thus avoiding the need of costly therapeutic switches of uncertain benefit.

Despite this presumed efficacy, some long-term safety concerns remain to be addressed. Unlike NB-UVB, PUVA has been associated with increased cutaneous malignancy rates (mostly squamous cell carcinomas, but also malignant melanoma), especially in skin types I and II patients exposed to >200-250 PUVA treatments.[18] Experimentally, UV photocarcinogenic damage appears to be potentiated with TNF-α inhibition[17] and in the interleukin (IL)-12 deficient mice.19 These and other biologic drug targets, such as IL-17 and IL-23 molecules, have anticarcinogenic effects and their blockade might dampen the elimination of precancerous skin cells.[17] Cases of melanoma have indeed been associated with anti-TNF,[20,21] and anti-IL12/23[22] targeted therapies. Furthermore, eruptive nevi have been described in biologic drug recipients.[23] In spite of this, with monotherapy the melanoma risk appears to be low for the biologic drug classes[24] and PUVA,[13] but the paucity of studies limits our knowledge about the safety of combining both modalities. In the present study, a patient developed a malignant melanoma. The uncontrolled nature of this investigation makes it impossible to establish this as a treatment-related malignancy. It could be a fortuitous finding, as a consequence of the strict dermatological observation due to the severe psoriatic disease, or a result of cumulative immunosuppressive treatments. In spite of this, malignant melanoma is an immunogenic cancer which has a more aggressive behavior and poorer prognosis in immunosuppressive states.[25] With PUVA (or NB-UVB, albeit probably to a lesser degree), critical antineoplastic immune pathways are impaired which might act synergistically with the biologic to foster a malignant growth. We strongly recommend a long-term follow-up with special emphasis on skin cancer examination in all subjects exposed to phototherapy (photochemoterapy) / biologic drug treatment combinations.

Our study design has some limitations. Firstly, our study cohort represents a highly selected population of hard-to-treat psoriatic patients. It is expected that a less recalcitrant psoriasis population would exhibit an even superior overall response profile to the studied combination regimens. Secondly, we acknowledge a significant heterogeneity among patients regarding previous phototherapy cumulative dose exposure, which might influence the results and adverse effects of the evaluated groups. This is due to the retrospective nature of our study. Thirdly, the small number of enrolled patients and the single-center population of the study are additional caveats. Lastly, it should be noted that a direct comparison between PUVA and NB-UVB as a rescue therapy is out of scope of this study. Whether significant differences exist (or not) in the clinical outcomes and safety of the two modalities of phototherapy studied, these should be addressed in future randomized, head-to-head comparative trials.

CONCLUSION

We add favorable evidence to PUVA and NB-UVB as effective options to restore a durable biologic drug response after a secondary failure. Increased cutaneous carcinogenicity is a concern with these combinations so a careful long-term follow-up is recommended, especially after photochemotherapy. Prospective controlled trials are warranted to clarify the role of this interesting approach in the modern era of improved biologic therapies.

Prémios / Apresentações: Parte deste trabalho foi apresentado em parte "XVII Congresso Nacional de Dermatologia e Venereologia" (1-3 Dezembr0 2017, Lisboa, Portugal). O trabalho recebeu o prémio de melhor comunicação oral.
Awards / Presentations: *The contents of this article were in part presented on the "XVII Congresso Nacional de Dermatologia e Venereologia" (1-3 December 2017, Lisbon, Portugal). The work was awarded as the best oral communication of the meeting.*

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.
Suporte financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Direito a privacidade e consentimento escrito: Os autores declaram que pediram consentimento para usar as imagens no artigo.
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial

Conflicts of interest: *The authors have no conflicts of interest to declare.*
Financing Support: *This work has not received any contribution, grant or scholarship.*
Confidentiality of data: *The authors declare that they have followed the protocols of their work center on the publication of data from patients.*
Privacy policy and informed consent: *The authors declare that have the written informed consent for the use of patient`s photos in this article.*
Protection of human and animal subjects: *The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).*

Proveniência e revisão por pares: Não comissionado; revisão externa por pares
Provenance and peer review: *Not commissioned; externally peer reviewed*

REFERENCES

1. Jungo P, Maul JT, Djamei V, von Felten S, Kolios AGA, Czernielewsk J, et al.Superiority in Quality of Life Improvement of Biologics over Conventional Systemic Drugs in a Swiss Real-Life Psoriasis Registry. Dermatology. 2016;232:655-63. doi: 10.1159/000455042.
2. Menter A, Papp KA, Gooderham M, Pariser DM, Augustin M, Kerdel FA, et al. Drug survival of biologic therapy

Artigo Original

in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Eur Acad Dermatol Venereol. 2016;30:1148-58. doi: 10.1111/jdv.13611.
3. Shalom G, Cohen AD, Ziv M, Eran CB, Feldhamer I, Freud T, et al. Biologic drug survival in Israeli psoriasis patients. J Am Acad Dermatol. 2017;76:662-9.e1. doi: 10.1016/j.jaad.2016.10.033.
4. Armstrong AW, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation. JAMA Dermatol. 2015;151:432-8. doi: 10.1001/jamadermatol.2014.3456.
5. Wolf P, Hofer A, Weger W, Posch-Fabian T, Gruber-Wackernagel A, Legat FJ. 311 nm ultraviolet B-accelerated response of psoriatic lesions in adalimumab-treated patients. Photodermatol Photoimmunol Photomed. 2011 ;27:186-9. doi: 10.1111/j.1600-0781.2011.00594.x
6. Wolf P, Hofer A, Legat FJ, Bretterklieber A, Weger W, Salmhofer W, et al. Treatment with 311-nm ultraviolet B accelerates and improves the clearance of psoriatic lesions in patients treated with etanercept. Br J Dermatol. 2009;160:186-9. doi: 10.1111/j.1365--2133.2008.08926.x.
7. Busard CI, Cohen AD, Wolf P, Gkalpakiotis S, Cazzaniga S, Stern RS, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. J Eur Acad Dermatol Venereol. 2018;32:245-253. doi: 10.1111/jdv.14583.
8. Lynde CW, Gupta AK, Guenther L, Poulin Y, Levesque A, Bissonnette R. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. J Dermatolog Treat. 2012;23:261-7. doi: 10.3109/09546634.2011.607795.
9. Park KK, Wu JJ, Koo J. A randomized, 'head-to-head' pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients. J Eur Acad Dermatol Venereol. 2013;27:899-906. doi: 10.1111/j.1468--3083.2012.04611.x.
10. Ara M, Gracia T, Pastushenko E. Etanercept combined with systemic drugs or phototherapy for treatment of psoriasis Actas Dermosifiliogr. 2015;106:180-8.
11. Gambichler T, Tigges C, Scola N, Weber J, Skrygan M, Bechara FG,et al.. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. Br J Dermatol. 2011;164:1383-6. doi: 10.1111/j.1365-2133.2011.10358.x.
12. De Simone C, D'Agostino M, Capizzi R, Capponi A, Venier A, Caldarola G. Combined treatment with etanercept 50 mg once weekly and narrow-band ultraviolet B phototherapy in chronic plaque psoriasis. Eur J Dermatol. 2011; 21:568-72. doi: 10.1684/ejd.2011.1330.
13. Calzavara-Pinton PG, Sala R, Arisi M, Rossi MT, Venturini M, Ortel B.Synergism between narrowband ultraviolet B phototherapy and etanercept for the treatment of plaque-type psoriasis. Br J Dermatol. 2013; 169:130-6. doi:10.1111/bjd.12277.
14. Bagel J. Adalimumab plus narrowband ultraviolet B light phototherapy for the treatment of moderate to severe psoriasis. J Drugs Dermatol. 2011 ;10:366-71.
15. Wolf P, Weger W, Legat FJ, Posch-Fabian T, Gruber-Wackernagel A, Inzinger M, et al. Treatment with 311-nm ultraviolet B enhanced response of psoriatic lesions in ustekinumab-treated patients: a randomized intraindividual trial. Br J Dermatol. 2012;166:147-53. doi: 10.1111/j.1365-2133.2011.10616.x.
16. Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maître M, et al. Efficacy of psoralen UV-A therapy vs. narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol. 2012;26:11-21. doi: 10.1111/j.1468-3083.2012.04519.x.
17. Gambichler T, Tigges C, Dith A, Skrygan M, Scola N, Altmeyer P, et al. Impact of etanercept treatment on ultraviolet B-induced inflammation, cell cycle regulation and DNA damage. Br J Dermatol. 2011;164:110-5. doi: 10.1111/j.1365-2133.2010.10099.x.
18. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol. 2009;60:1001-17. doi: 10.1016/j.jaad.2008.12.031.
19. Maeda A, Schneider SW, Kojima M, Beissert S, Schwarz T, Schwarz A. Enhanced photocarcinogenesis in interleukin-12-deficient mice. Cancer Res. 2006;66:2962-9.
20. Fulchiero GJ Jr, Salvaggio H, Drabick JJ, Staveley-O'Carroll K, Billingsley EM, Marks JG, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. J Am Acad Dermatol. 2007;56:S65-7.
21. Kouklakis G, Efremidou EI, Pitiakoudis M, Liratzopoulos N, Polychronidis ACh. Development of primary malignant melanoma during treatment with a TNF-α antagonist for severe Crohn's disease: a case report and review of the hypothetical association between TNF-α blockers and cancer. Drug Des Devel Ther. 2013;7:195-9. doi: 10.2147/DDDT.S41889.
22. Ehmann LM, Tillack-Schreiber C, Brand S, Wollenberg A. Malignant melanoma during ustekinumab therapy of Crohn's disease. Inflamm Bowel Dis. 2012;18:E199-200. doi: 10.1002/ibd.21877.
23. Bovenschen HJ, Tjioe M, Vermaat H, de Hoop D, Witteman BM, Janssens RW, et al. Induction of eruptive benign melanocytic naevi by immune suppressive agents, including biologicals. Br J Dermatol. 2006;154:880-4.
24. Mercer LK, Askling J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis. 2017;76:386-91. doi: 10.1136/annrheumdis-2016-209285.
25. Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. Mayo Clin Proc. 2012t;87:991-1003. doi: 10.1016/j.mayocp.2012.04.018.