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ORIGINAL ARTICLE

New-onset vitiligo and progression of pre-existing vitiligo during treatment with biological agents in chronic inflammatory diseases

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Abstract

Background The development of vitiligo during treatment with biological agents is an unusual event and only a few isolated cases have been reported.

Objectives To describe the clinical characteristics and evolution of patients developing new-onset vitiligo following initiation of a biological agent for chronic inflammatory disease; and also to report the clinical course of pre-existing vitiligo under biological therapy.

Methods This nationwide multicentre, retrospective study, carried out between July 2013 and January 2015, describes the characteristics of a large series of 18 patients (psoriasis $N = 8$, inflammatory rheumatic diseases $N = 8$, ulcerative colitis $N = 1$, uveitis $N = 1$) who developed new-onset vitiligo while receiving a biological agent.

Results TNFα inhibitors were the most common biological agent involved (13/18) while anti-IL-12/23 and anti-IL-17 agents or abatacept were less common (4/18 and 1/18 respectively). Mean duration of biological agent exposure before vitiligo onset was 13.9 ± 16.5 months. Outcome was favourable for most patients (15/17) while maintaining the biological agent. Data were also collected for 18 patients (psoriasis $N = 5$, inflammatory rheumatic diseases $N = 10$, inflammatory bowel diseases $N = 2$, SAPHO $N = 1$) who had pre-existing vitiligo when treatment with a biological agent started (TNFα inhibitors $N = 15$, ustekinumab $N = 1$, rituximab $N = 1$, tocilizumab $N = 1$). Vitiligo progressed in seven patients and was stable or improved in eight cases.

Conclusion Vitiligo may thus emerge and/or progress during treatment with various biological agents, mainly TNFα inhibitors and could be a new paradoxical skin reaction. *De novo* vitiligo displays a favourable outcome when maintaining the biological agent, whereas the prognosis seems worse in cases of pre-existing vitiligo.

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Conflicts of interest

L. Méry-Bossard has received speaker honoraria from AbbVie and Pfizer. F. Maccari is a consultant for Janssen-Cilag and has received speaker honoraria from AbbVie and Janssen-Cilag. J.L. Perrot is a consultant for AbbVie, Janssen-Cilag, MSD and Novartis. Z. Reguiai is a consultant for Janssen-Cilag and Pfizer; has been an investigator for AbbVie, Novartis, Pfizer; has received speaker honoraria from AbbVie, Janssen-Cilag and Pfizer. M.L. Sigal has received speaker honoraria from Janssen-Cilag. T. Boyé has received speaker honoraria from

AbbVie, Novartis and Pfizer. A. Grasland has received speaker honoraria from AbbVie, BMS, Pfizer, Roche. D. Jullien is an advisory board member and received speaker honoraria from AbbVie, Janssen-Cilag, Lilly, Novartis and Pfizer; and is investigator for Amgen. K. Bagny, G. Chaby, A. Khemis, H. Marotte, M.Avenel-Audran, J.Gillard ans E. Toussirot declare no conflict of interest in this article.

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Introduction

Tumour necrosis factor alpha (TNFα) inhibitors have been used for many years in the treatment of different chronic inflammatory diseases including inflammatory bowel diseases, inflammatory rheumatic diseases and psoriasis. Anti-lymphocyte B (rituximab) and costimulatory blockers (abatacept, a CTLA-4 fusion protein) are also available to treat rheumatoid arthritis. More recently, biological therapies targeting the Th17/IL-12/23 pathway have been developed and ustekinumab, an anti-p40 IL-12/23 product, is currently on the market for the treatment of psoriasis and psoriatic arthritis. All these different biological agents have been associated with various adverse events affecting the skin, with a frequency ranging from 10% to 60%.[1–3] In a 5-year prospective analysis of patients with chronic inflammatory arthritis, the main risk factors for cutaneous events under TNFα inhibitors were identified as advanced age, female sex, diagnosis of rheumatoid arthritis, disease activity and the use of infliximab.[2] Psoriasis is among the most widely reported cutaneous side-effect of anti-TNFα therapy and is considered to occur as a paradoxical skin reaction.[4]

Vitiligo is a common depigmenting disorder affecting around 0.5% of the world population.[5] The development of new-onset vitiligo upon initiation of a biological agent is an unusual event and only a few isolated cases have been reported.[1,6–12] In parallel, biological agents given for an autoimmune disease may potentially influence the outcome of pre-existing vitiligo. We thus conducted this study to describe the clinical characteristics and evolution of patients developing new-onset vitiligo following initiation of a biological agent for chronic inflammatory disease. We also reported the clinical course of pre-existing vitiligo under biological therapy.

Patients and methods

Study design

This study was carried out between July 2013 and January 2015. This was an observational retrospective, nationwide multicenter study. A call for new cases of vitiligo, following initiation of biological treatment (anti-TNFα [infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept], anti-IL-6 [tocilizumab], anti-CD20 [rituximab], anti-IL-1 [anakinra], anti-IL-12/23 [ustekinumab] and anti-IL17 [secukinumab]) was sent to the members of the French specialist networks « *Resopso* » (dermatologists), the French Society of Dermatology (SFD) and '*Club Rhumatismes et Inflammation*' (CRI) (rheumatologists and specialists in internal medicine), using a standardized questionnaire available on specific website. Patients with pre-existing vitiligo and receiving a biological agent for another chronic inflammatory disease were also recorded as a comparative group. The diagnosis of vitiligo had to be confirmed by a dermatologist. For pre-existing vitiligo, the changes in skin pigmentation also had to be evaluated by a dermatologist. Demographic characteristics (age, sex) and clinical data (medical history, underlying inflammatory disease, biological agent, time frame between starting treatment with a biological agent and onset/modification of vitiligo), type (localized, generalized, segmental) and site(s) of vitiligo, outcome of vitiligo and prescribed treatments were recorded for all patients.

Table 1 Clinical characteristics and outcome of patients developing *de novo* vitiligo and patients with pre-existing vitiligo while receiving a biological agent for a chronic inflammatory disease

	***De novo* vitiligo *N* = 18**	**Pre-existing vitiligo *N* = 18**
Sex (M/F), *n*	11/7	9/9
Age (years), mean ± SD [median]	42.8 ± 12.8 [43.5]	53.0 ± 14.7 [56.5]
Underlying inflammatory disease, *n*		
Psoriasis	8	5
Psoriatic arthritis	/	3
Rheumatoid arthritis	4	6
Ankylosing spondylitis	4	1
Ulcerative colitis	1	1
Crohn's disease	/	1
Pan uveitis	1	/
SAPHO	/	1
Previous medical history, *n*		
Lupus	1	1
Diabetes	2	1
Crohn's disease	1	/
Thyroiditis	/	4
Familial history of vitiligo, *n*	/	1

Table 2 Vitiligo history

	De novo vitiligo *N* = 18	Pre-existing vitiligo *N* = 18
Biological agent, *n*		
Adalimumab	8	7
Infliximab	3	4
Etanercept	/	4
Certolizumab	2	/
Ustekinumab	3	1
Rituximab	/	1
Tocilizumab	/	1
Abatacept	1	/
Secukinumab	1	/
Time frame between initiation of biological agent and vitiligo appearance/modification (months), mean ± SD [median]	13.9 ± 16.5 [10]	13.8 ± 22.9 [14.5]
Site of vitiligo (*n* = 15), *n*	(known for 15 cases)	(known for 14 cases)
Disseminanted	/	2
Trunk and limbs	10	10
Face/head	3	2
Peliosis	1	/
Leucotrichia	1	/
Maintenance of the biological agent (yes), *n* (%)	12 (66.7)	17 (94.4)
Outcome, *n* (%)*		
Progression	2 (11.8)	7 (43.7)
Stable	9 (52.9)	8 (50.0)
Repigmentation	6 (35.3)	1 (6.2)

*Lacking data: one in the '*de novo*' group, two in the 'pre-existing' group.

Results

First group: new-onset vitiligo

Eighteen new cases of vitiligo were reported by 12 French hospitals. Eleven patients (61%) were male and the mean age was 42.8 ± 12.8 years (median: 43.5, range: 17–69). Non-segmental vitiligo was diagnosed in 17 patients and leucotrichia in one. No patient had any previous personal/family history of depigmenting or thyroid disease but one had developed paradoxical psoriasis during a previous course of biological treatment. Four others had concomitant chronic inflammatory disease (Table 1). The underlying inflammatory diseases requiring the biological agent were psoriasis (n = 8), rheumatoid arthritis (n = 4), ankylosing spondylitis (n = 4), ulcerative colitis (n = 1) and panuveitis (n = 1). Adalimumab was the most common biological agent involved (N = 8), followed by infliximab (N = 3) and ustekinumab (N = 3), while abatacept (N = 1) and secukinumab (N = 1) were less commonly used (Table 2). The biological agent was given as a first-line treatment to twelve patients. Four of them had concomitant therapy with leflunomide (N = 1), methotrexate (N = 1) or oral corticosteroids (N = 2). Mean time between biological agent initiation and vitiligo onset was 13.9 ± 16.5 months (median: 10, range 1–72). Vitiligo was localized, and usually affected the trunk, limbs or face (Figs 1–3). In 12/18 (66.6%) patients, the biological agent was continued without worsening of vitiligo. Fifteen out of 18 patients (83.3%), experienced stabilization or partial repigmentation, while the skin disease progressed in two cases (outcome was unknown in one case). Skin depigmentation was treated by topical application in six cases (dermocorticosteroids N = 4, tacrolimus N = 2). Biological agent was switched in three cases because of uncontrolled underlying inflammatory disease (two from adalimumab to etanercept and one from infliximab to ustekinumab), without progression of vitiligo. In three cases, the biological agent (infliximab N = 2, abatacept N = 1) was permanently

Figure 1 Vitiligo onset 1 month after adalimumab for psoriasis (first-line biotherapy).

Figure 2 Repigmentation after switch from adalimumab to ustekinumab.

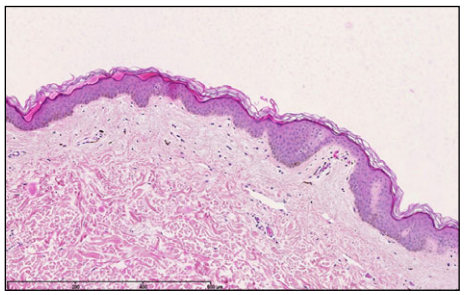

Figure 3 Skin biopsy of the same patient: hypopigmentation of basal lining cells and decreased number of melanocytes.

stopped. Skin depigmentation remained stable in two of these patients and improved in one during follow-up.

Second group: pre-existing vitiligo

Eighteen patients had pre-existing non-segmental and stable vitiligo at the time of starting treatment with a biological agent. They were declared by 12 different centres. Nine patients (50%) were male and the mean age was 53.0 ± 14.7 (median: 56.5, range: 20-72). Four patients had thyroid disease and one had a family history of vitiligo (Table 1). Mean duration of vitiligo before starting treatment with a biological agent was 257.0 ± 170.2 months (median: 238, range: 7–604 months). The inflammatory diseases requiring a biological agent were: psoriasis (N = 5), rheumatoid arthritis (N = 6), psoriatic arthritis (N = 3), ankylosing spondylitis (N = 1), SAPHO syndrome (N = 1), ulcerative colitis (N = 1) and Crohn's disease (N = 1). For 11 of the patients, this was the first time a biological agent had been used. The biological agents used were TNFα inhibitors in 15 cases (adalimumab N = 7; infliximab N = 4; etanercept N = 4), while the others received ustekinumab (N = 1), rituximab (N = 1) or tocilizumab (N = 1) (Table 2). The main sites of vitiligo were the trunk and limbs (71.4%). After initiating the biological agent, progression of vitiligo was observed in seven cases, stability in eight and one case of partial repigmentation was observed (outcome was unknown in two cases). Concomitant therapies were known for ten patients (unknown for eight patients): methotrexate was associated with the biological agent in three patients in the stable group and one in the worsening group, the others having no associated therapy. Vitiligo progression was observed in patients under adalimumab (N = 4), infliximab (N = 2) and etanercept (N = 1). The mean delay between the start of treatment with the biological agent and changes in skin pigmentation was 13.8 ± 22.9 months (median:14.5). The treatment was maintained in 17 cases and was stopped for one patient. Skin depigmentation was treated by dermocorticoids in one case, and by topical tacrolimus in two cases. No patient was switched to another biological agent.

The mean follow-up time after vitiligo appeared (first group) or progressed/improved/stabilized (second group) was 32 ± 14 months. This was similar in the two groups.

Discussion

There have only been a few studies reporting a link between the use of a biological agent in inflammatory diseases and the development of *de novo* vitiligo and/or progression of pre-existing vitiligo.[1,6–12] We describe here the largest series of 18 patients with vitiligo that appeared during biological therapy (first group) and in parallel, a group of 18 patients who had pre-existing vitiligo at the time of starting a biological agent, with depigmention that progressed in roughly half of them (second group).

The patients in the first group were predominantly male, but they were older than those with common vitiligo.[13] In this group, a small number had an associated autoimmune condition while thyroid disease was more common in the second group. New-onset vitiligo under a biological agent is considered to be a rare event estimated to occur in 1/5437 patients in one study.[14] Most reports of *de novo* vitiligo under a biological agent have been described as isolated cases associated with the use of infliximab[1,6–9] or adalimumab.[11,12] There have been two cases in which the type of biological agent was not specified.[10] Skin depigmentation appeared within 6–8 months after starting the biological agent. This is shorter than in our first group of patients. New-onset vitiligo in our series was associated with the use of different biological agents but TNFα inhibitors were overrepresented (72.2%), only with monoclonal antibody (no cases were observed with etanercept), while anti-IL-12/23 or anti-IL-17 agents were less well represented (22.2%). However, TNFα inhibitors are currently the most widely prescribed biological agent in different inflammatory diseases and this could have influenced the results. Most of our patients (N = 12) continued their biological agent and their skin disease improved or stabilized, indicating that *de novo* vitiligo had a favourable outcome and prognosis. However, the skin lesions were treated by topical agents in six cases, which may have influenced this outcome.

Pre-existing vitiligo may also change under exposure to a biological agent. Indeed, in our second group, vitiligo worsened in half of the patients, while the others experienced stability or even improvement. Associated inflammatory conditions and a family history of depigmenting disorder are more often observed in this group compared to the first one. Again, in the second group, TNFα inhibitors were mainly associated with progression of vitiligo with a predominance of monoclonal antibodies (N = 6 vs. only one case under etanercept).

The mechanism by which a biological agent may be associated with the development/progression of vitiligo is unknown. TNFα is a pro-inflammatory cytokine that plays a central role in the pathogenesis of vitiligo.[13,14] Indeed, abnormal expression of TNFα has been described in lesional vitiligo skin, with a level of expression related to disease severity.[15] TNFα inhibits melanocyte differentiation from stem cells and melanocyte function.[16] TNFα also destroys melanocytes through induction of apoptosis.[17] Conversely, TNFα can activate and induce proliferation of T regulatory cells (Treg) and T reg abundance is markedly reduced in the skin of vitiligo patients.[18] Therefore, blocking the TNFα pathway may be useful in lesional vitiligo skin.[19] However, results on the effects of TNFα inhibitors in patients with vitiligo are not convincing. Indeed, small series of patients receiving infliximab, adalimumab or etanercept showed no or mild improvement of depigmenting lesions.[20–22] On the contrary, our series and previous reported cases illustrated well that TNFα inhibitors and other biological agents may be associated with the emergence/progression of vitiligo. The underlying mechanisms for explaining this unexpected reaction are that the biological agent may lead to local changes

to the cytokine balance and/or activation of alternative pathways such as type I interferon, as is described for psoriatic-induced lesions.[4] Inhibiting TNFα can also be associated with a decrease in T reg production and activation and less T reg skin homing that allow T-cell autoreactivity against melanocytes.[18,23] IFN γ is another cytokine that plays a central role in vitiligo by suppressing T reg function and inducing melanocyte apoptosis.[24,25] PBMCs from patients with vitiligo display high expression of t-bet and IFNγ.[26] A dual role for TNFα inhibitors on Th1/Th2 cytokine balance has been reported in spondyloarthritis, reducing (infliximab) or enhancing (etanercept) IFNγ production.[27,28] Tofacitinib, an anti JAK1/2 synthetic drug used in rheumatoid arthritis, may improve vitiligo.[29] IFNγ signal transduction occurs through JAK1/2, and IFNγ induced the expression of CXCL10 chemokine in keratinocytes that can interact with CXCR3 on autoreactive CD8+ T cells. The IFNγ/JAK 1/3/chemokine CXCL10-CRCX3 pathway seems to be a key determinant in vitiligo development. NALP1 genetic variants have been linked to vitiligo and thus, another hypothesis is that the biological agent may interfere with innate immunity in selected and genetically predisposed patients.[30, 31]

Co-occurrence of vitiligo with inflammatory diseases is well described[5,13,32,33] and thus, the development/worsening of skin depigmentation may be coincidental and related to the underlying disease. However, predisposing factors such as family history were poorly represented in our two series. Three patients in the first group had to switch biologic because of the uncontrolled inflammatory disease. Thus, in these three cases, we may consider that the underlying uncontrolled disease could promote vitiligo onset.

Whether or not the biological agent should be discontinued at vitiligo onset and/or worsening is a relevant issue. Most of our patients with *de novo* vitiligo had a favourable outcome while continuing to take the same biological agent. However, some of the patients had concomitant topical treatment. Considering our series of vitiligo onset, we can thus recommend continuing the biological agent. A worse outcome was observed in 44% of the patients with pre-existing vitiligo. It is known that vitiligo is associated with psychological consequences and has an impact on self- esteem. Thus, the benefits of the biological agents for the underlying chronic inflammatory disease must be balanced with the consequences of skin depigmentation in terms of quality of life. In this sense, assessing the activity of the inflammatory disease and using a quality of life questionnaire may be helpful.

It has recently been suggested that TNFα inhibitors have different effects depending on the subgroup of vitiligo.[14] Indeed, stabilization of disease or repigmentation may be obtained with TNFα inhibitors in patients with progressive vitiligo. However, worsening can occur if the skin disease is stable. This is consistent with the outcomes observed in our second group of patients who experienced different outcomes. However, the disease activity and potential of vitiligo to progress has not been specifically evaluated in our series using adapted outcome measures.

Our study had limitations; it was retrospective and was small in size. However, it is the largest series reported to date that described clinical situations in real practice, providing informative data for clinicians.

Conclusion

New-onset vitiligo or progression of pre-existing vitiligo is a rare but not exceptional event that can occur with TNFα inhibitors and other biological agents. Whether this could represent a new paradoxical skin reaction or not remains an open question. *De novo* vitiligo displays a favourable outcome when the biological agent was maintained, while the prognosis seems worse in cases of pre-existing vitiligo which progressed. Thus, clinicians must be aware of this unexpected adverse event in skin, and should closely observe and evaluate their patients' skin when introducing a biological agent, especially in cases of pre-existing depigmentation.

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