Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Breakthrough Psoriasis in Patients Receiving Biologicals

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Background: Biological therapies, including TNF-alpha, IL12/23, IL17 and IL23 antagonists, adequately control a very high number of patients with moderate-to-severe psoriasis with an excellent long-term safety profile. However, on occasion, patients on biological therapy with stabilized disease or complete remission report episodes of sudden breakthrough psoriasis.

Aim: To study prospectively in a monocentric tertiary setting, the clinical characteristics of patients presenting a sudden breakthrough psoriasis although completely stabilized (PASI 90–100) under biological therapy.

Materials and Methods: Psoriasis patients treated by biological therapies achieving PASI 90–100 and with stabilized disease for at least 6 months were invited to enter the follow-up study for 5 years. The clinical features of patients presenting a breakthrough psoriasis were described as well as the rescue therapies and outcomes.

Results: From the total cohort of 1121 patients with psoriasis receiving biologicals, 985 patients responded to the inclusion criteria. After 5 years, 10/882 cases (1,13%) of breakthrough psoriasis were identified. Two cases were induced by the Köbner phenomenon and 8 cases by severe psychological stress. Rescue therapies included topical very potent corticosteroids or additional injections of the biological. Two patients recovered spontaneously when the stressful event was resolved. In none of the cases, there was a consistency between the breakthrough event and the next scheduled injection, nor the duration of the exposure to the treatment. No biological class or agent could be systematically incriminated.

Conclusion: Breakthrough psoriasis is an exceptional event among patients with stabilized psoriasis using biologicals, either triggered by the Köbner phenomenon or by severe psychological stress. The pathogenesis of the breakthrough events could be linked to stress- or Köbner-related immunomodulation, permitting breakthrough psoriasis lesions to appear.

Keywords: psoriasis, biologicals, TNF-alpha, IL17, IL23, Köbner phenomenon, stress

Introduction

Psoriasis vulgaris is considered as an immune-mediated skin and/or joint disease. The quality of life (QoL) of psoriasis patients is severely impacted. Fortunately, the arrival of the biological therapies, including the TNF-alpha antagonists (etanercept, adalimumab, infliximab, certolizumab), the IL12/23 antagonist (ustekinumab), the IL17 antagonists (secukinumab, ixekizumab, brodalumab, bimekizumab) and the IL23 antagonists (guselkumab, tildrakizumab, risankizumab) led to a very impressive improvement and even complete resolution of psoriasis in a high number of adult[1–3] and paediatric patients.[4] In addition, the long-term safety profile of these treatments and their long-term persisting efficacy permit sustained control of psoriasis in a very high percentage of patients.[1–4]

The triggering factors of new-onset psoriasis and psoriasis flares are numerous, heterogenous and often multifactorial.[5–9] They are not similar for all patients and may even vary over time in an individual patient. Classic triggering factors include several common medications, such as beta-blocking agents, mechanical friction (Köbner phenomenon),[7–9] cutaneous infections (*Staphylococcus*), environmental influences such as pollution, lifestyle and psychological stress,[5,10] as well as hormonal and metabolic alterations. More recently described risk factors comprise biological drugs (inducing paradoxical psoriasis), immunotherapies (immune checkpoint inhibitors) for cancer, Covid-19

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infection and some vaccines (vaccination for influenza, pneumococcal pneumonia, tetanus, diphtheria, yellow fever, and Covid-19 mRNA).[5,6]

Addressing these factors may improve treatment outcomes, for example, acting on psychological stress can significantly help psoriasis patients to cope with the social consequences of their disease.[11–13]

Despite the very high number of psoriasis patients successfully treated by biologicals with long-term sustained results, some of them report, on occasion, sudden flares or breakthrough of psoriasis lesions whilst being compliant with the injection schemes of biological anti-psoriasis treatments.

In this five-year prospective observational study including psoriasis patients with long-term controlled psoriasis by using biologicals, cases with a sudden-onset breakthrough psoriasis were searched for. The demographic features and causes of the breakthrough psoriasis were analysed, as well as the therapeutic management.

Materials and Methods

This study was performed in accordance with the Helsinki convention on human rights. The institutional ethic committee (Ethical Committee CHU de Liège, 707) approved the observational design of the study. The patients were informed about the procedures, and all signed an informed consent form.

Patients with moderate-to-severe plaque-type psoriasis receiving biological therapies (etanercept, adalimumab, infliximab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab and risankizumab) were retrieved in our institutional psoriasis data base at baseline. Patients having achieved PASI 90–100 and with stable disease for at least 6 months, with no flares, were asked to participate in the study (Figure 1).

Other types than plaque-type psoriasis (psoriasis vulgaris) were excluded. Patients were also excluded from the study if they deviated from the recommended treatment schedules during the study (tapering of injections, failed injections). Patients were excluded from the study if they presented a progressive loss of treatment efficacy. Pregnancy during the study was also a reason to interrupt the study participation. The introduction of potential psoriasis-inducing or psoriasis-exacerbating medications during the study period was also a reason to interrupt the study participation, as well as a significant weight gain during the study. Vaccination-linked recurrences during the study period were also excluded.

Follow-up visits were scheduled at the discretion of the case-managing dermatologist, usually twice per year as per reimbursement issues.

The study (first patient in) started in January 2018 and ended July 2024 (last patient out).

At baseline, patients were educated and trained on the recognition of sudden unexpected skin lesions, and this information was repeated during follow-up visits. Breakthrough psoriasis was defined as the sudden appearance of typical (1–2 weeks) psoriasis skin lesions on any site of the integument during the observation period (absolute PASI of 3–5).

The participating patients were instructed to immediately report to their dermatologist in the event of a breakthrough psoriasis.

From the cases responding to these criteria the following clinical features were recorded, including age, gender, duration of psoriasis, professional occupation, biological treatment, interval between the instauration of the biological agent and the breakthrough event, moment of the appearance of the breakthrough psoriasis in the treatment schedule, type of trigger and rescue therapy if required.

Rescue therapy for the breakthrough psoriasis cases was determined and initiated at the discretion of the case-managing dermatologist.

Results

A flow chart illustrates the inclusion process (Figure 1). At baseline, the total cohort of patients receiving a biotherapy for psoriasis, including TNF-alpha antagonists (etanercept, adalimumab, infliximab, certolizumab), IL12/23 antagonist (ustekinumab), IL17 antagonists (secukinumab, ixekizumab, brodalumab) and IL23 antagonists (guselkumab, risankizumab), included 1121 patients. The number of patients presenting a stable disease for at least 6 months included 985 patients, of which 945 accepted to enter the observational study (Table 1). The total number still present at the study closure at 5 years was 882 patients. The total number of patients responding to the criterion of sudden breakthrough psoriasis during the 5-year study period was 10. From these latter patients, Table 2 presents the demographic features

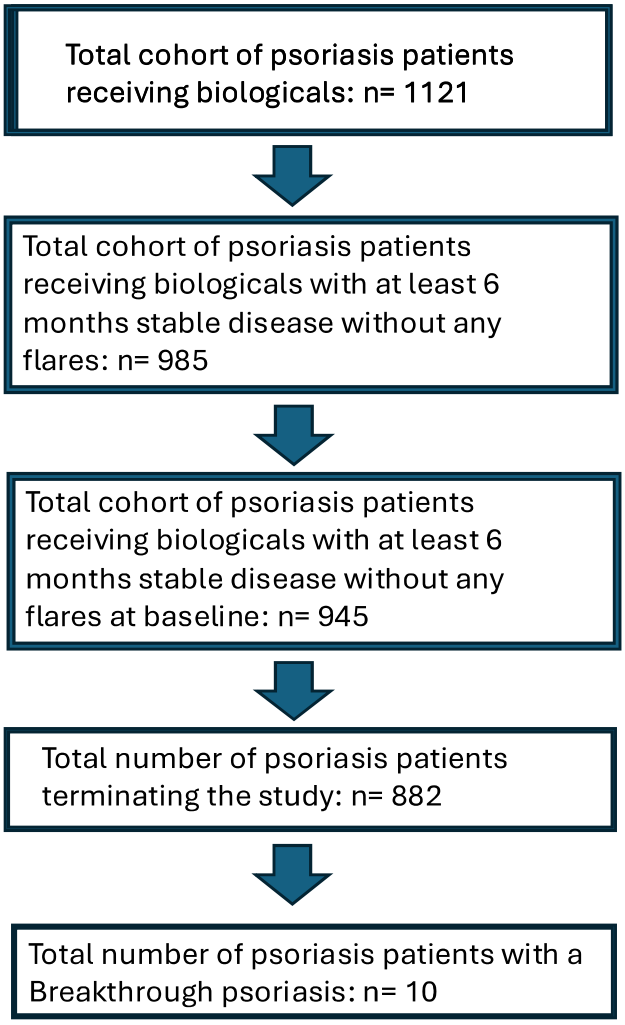

Figure 1 Study flow design and number of patients.

(age, gender, duration of psoriasis prior to entering the study, the biological treatment, the interval between the instauration of the biological agent and the breakthrough event, the profession, the type of psoriasis trigger, the type of psoriasis recurrence, as well as the rescue therapy with its outcome. Table 1 shows the numbers of the individual biologicals and biological classes as well as the percentage of breakthrough cases.

The most frequently used biological agents were the IL23 antagonists (n = 563), followed by the IL17 antagonists (n = 208), the TNF-alpha inhibitors (n=109), and the IL12/23 antagonist (n = 105)(Table 1).

All the patients presented a long personal history of plaque-type psoriasis.

No specific type of biological agent nor class, nor age or gender could be associated with breakthrough psoriasis. None of the breakthrough psoriasis cases discontinued nor interrupted the biological treatment after the breakthrough event. None of the patients was switched to another treatment option.

Furthermore, there was no correlation between the interval after the last injection of the biological and the breakthrough event. There was no link between the total duration of exposure to the biological agent and the breakthrough event.

The stressful events were either of professional origin or caused by personal life items (Table 2).

For the Köbner-linked breakthrough cases a topical very potent topical treatment was prescribed, probable to the localized areas of recurrence. The stress-linked breakthrough cases were often treated by a supplementary injection of the biological the patient was already treated with. The outcome was generally favourable.

Figure 2 illustrates the 2 clinical cases responding to the Köbner effect whilst on biologicals with stable remission.

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Table 1 Total Number of Different Biologicals at the End of the Study as Well as the Percentage of Breakthrough Cases

Biological Agent	Total Number of Psoriasis Patients Receiving Biologicals with at least 6 Months Stable Disease without any Flares	Total Number of Psoriasis Patients Receiving Biologicals with at least 6 Months Stable Disease without any Flares at Baseline	Total Number of Psoriasis Patients Terminating the Study	Total Number of Psoriasis Patients with a Breakthrough Psoriasis	Cases of Breakthrough Psoriasis in %
Etanercept	5	3	0	0	0%
Infliximab	3	2	0	0	0%
Adalimumab	101	99	97	1	1.03%
Ustekinumab	105	103	99	1	1.01%
Secukinumab	104	101	98	1	1.02%
Ixekizumab	101	96	89	1	1.12%
Brodalumab	3	3	0	0	0%
Guselkumab	374	357	334	4	1.2%
Risankizumab	189	181	165	2	1.21%
TNF alpha inhibitors	109	104	97	1	1.03%
IL12/23 inhibitor	105	103	99	1	1.01%
IL17 inhibitors	208	200	187	2	1.07%
IL23 inhibitors	563	538	499	6	1.2%
Total	985	945	882	10	1.13%

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Table 2 Demographics, Clinical Data and Rescue Therapy, of the Breakthrough Cases

N	S A	Duration Psoriasis	Biol	Profession	Trigger	Type of Recurrence	Inter	Rescue Therapy	Rescue Therapy Outcome
1	F 75	More than 20 years	Gus	Retired teacher	Severe psychological stress (unexpected death of her husband)	Psoriasis capitis	27 mo	Clobetasol propionate 0.05% lotion 2/day 15 days	Successful
2	M 72	More than 20 years	Gus	Retired lumberjack	Wood chopping for firewood for long hours (Figure 2a)	Palmar psoriasis of his right hand (heavy ax)	65 mo	Betamethasone and calcipotriol ointment under occlusion	Successful
3	F 62	Since childhood	Gus	Caregiver at a home for elderly people	Severe psychological stress (implementation of new work regulations)	ES plaques of the dorsal aspect of the hands, ears, vertex and mammary folds	37 mo	Supplementary injection of Gus	Successful after 2–3 weeks
4	M 63	At least 30 years	Ris	Agricultural worker	Wearing a heavy toolbelt for renovation works on a cow shed (Figure 2b)	ES lesions facing the toolbelt	28 mo	Supplementary injection of Ris	Partially effective
5	F 38	At least 12 years	Sec	Nursery school-teacher	Severe psychological stress (death threats to her baby girl by her ex-husband)	Recurrence of several of her usual ancient psoriasis plaques	87 mo	Progressive spontaneous healing after legal hearing	Judge ordered legal ban of visits
6	F 82	At least 40 years	Ada	Retired housewife	Severe psychological stress (unexpected sudden death of her daughter)	Recurrence of hand, elbow, legs and scalp psoriasis	126 mo	Supplementary injections of Ada 40 mg	Successful after 1 month
7	M 33	At least 14 years	Gus	Financial engineer	Stressful event (work, new tight deadline)	Relapse of several preexisting areas	53 mo	Supplementary injection of Gus	Successful
8	F 59	At least 28 years	Ris	Police officer	Stressful event (work, lethal car accident)	Recurrence of several preexisting areas of psoriasis	39 mo	Supplementary injection of Ris	Successful
9	M 75	At least 25 years	Ust	Retired farmer	Stress in the family (announcement of divorce of his child)	Several ES lesions on the extremities and the back	87 mo	PUVA therapy	Partially successful
10	M 34	Since childhood	Ixe	Bank employee	Change of computer program due to sudden merge with another bank	Severe psoriasis capitis recurrence	28 mo	Spontaneous improvement one month later	Successful

Abbreviations: N, Number of patient; S, sex; A, age; M, male; F, female; Biol, biological agent; Mo, months; Inter, Interval between instauration of the biological agent and the breakthrough event; Gus, Guselkumab; Sec, Secukinumab; Ada, Adalimumab; Ixe, Ixekizumab; Ust, Ustekinumab; Ris, Risankizumab; ES, Erythemato-squamous.

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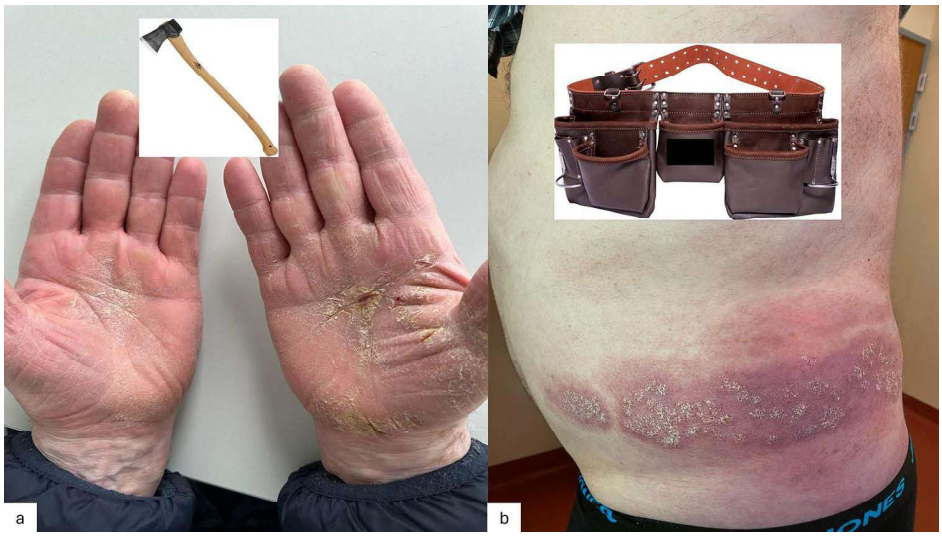

Figure 2 Clinical cases responding to the Köbner effect whilst on biologicals with stable remission. Case 2 (**a**): woodchopping with a heavy axe, inducing palmar psoriasis. Case 4 (**b**): wearing a heavy toolbelt inducing a belt-like psoriasis.

Discussion

This prospective observational study shows that in our centre, a high proportion of psoriasis patients are treated with IL23 antagonists, roughly 2.5 times more than the IL17 antagonists and 5 times more compared to the TNF-alpha inhibitors and the IL12/23 inhibitor. This may be related to the tertiary setting of the study, reimbursement issues, or prescription habits. However, it reflects relatively well the real-world data that have been published recently for Belgium.[14]

This study demonstrates that despite the very high number of patients with plaque-type psoriasis that were successfully treated with biological agents on the long term, about 1% of the patients may experience events of breakthrough psoriasis. The identified triggers were either friction-induced (Köbner phenomenon) recurrences of psoriasis or linked to sudden, severely stressful events. Hence, breakthrough psoriasis could represent an event to be retained among the already published long-term safety data.[15–17]

The real Köbner effect is defined as the appearance of a skin lesion corresponding to a previously known dermatosis on a non-lesional skin area by friction or traumatism. Furthermore, the event should be reproducible.[9,18] The 2 cases described here respond to the definition of a real Köbner effect, according to the classification of Boyd and Neldner.[18] There are no specific recommendations for the treatment of these cases, but they respond to conventional anti-psoriasis agents, as shown in our patients.

Stress is a very important factor in the pathogenesis and clinical expression of psoriasis. Acting on stress factors can improve psoriasis outcome, even without any medical interventions, such as demonstrated by the 5–20% clinical improvements in placebo groups in studies evaluating the efficacy of anti-psoriatic and anti-psoriatic arthritis agents.[19,20] A recent clinical trial revealed that for some psoriasis patients the understanding of the relationship between psychological factors and symptoms of their psoriasis helped to improve their skin disease.[12] Another study also underlined the importance of adequate management of stress factors in patients experiencing high psychosocial stress during the treatment of psoriasis.[13] Increasing awareness of psoriasis associated comorbidities, including medical and psychological issues, should be part of the holistic approach of treating psoriasis patients.[11]

The importance of reducing the stress factor is also well illustrated by the cases 5 and 10. These patients were clearly aware of the stressful events as trigger for their recurrence but as these events were transient, they did not ask for specific treatment. Indeed, without additional therapy, they reached complete remission soon after the resolution of the triggering stress events.

In this study, the breakthrough psoriasis lesions were treated at the discretion of the case-managing dermatologist. A supplementary dosing of the biological was frequently used with a successful outcome in 5/5 cases. It is stressed out that this rescue therapy is an off-label practice.

Whether the rescue therapy or the waning of the stress event was responsible for the healing of the breakthrough psoriasis remains difficult to determine.

The pathogenesis of these breakthrough cases could be explained by the fact that either the patients display a kind of neuro-inflammatory/immunological threshold above which their psoriasis is controlled by the biological agent, but where either stress or Köbner events may result in crossing the threshold level followed by recurrence. Another possibility is the stimulation by the triggers of other or alternative pathways disrupting the functioning of the given biological, followed by new lesions.

The breakthrough events could not be related to a specific class of biological agents, nor to individual biological agents.

Conclusion

This study reveals that some biological-treated psoriasis patients with stabilized disease or achieving complete remission may still experience a sudden breakthrough of psoriasis, either triggered by the Köbner phenomenon or by severe psychological stress. Patient education on identifying their triggering factors and the treatment of breakthrough lesions is recommended in the holistic approach of individual psoriasis management. Both topical treatments and additional injections of biological agents were usually successful for mastering the breakthrough psoriasis lesions.

Data Sharing Statement

All the data are described and available in this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest in this work.

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