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REVIEW ARTICLE

Biologic therapy and paradoxical reactions

Guillermo J. Sánchez-Rodríguez and Anna López-Ferrer*

Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

Abstract

Paradoxical reactions are defined as adverse effects that manifest as a de novo appearance or the exacerbation of a condition that commonly responds to a certain class of drug. A well-known example of paradoxical reaction is the debut of psoriatic eruptions when patients undergo anti-tumor necrosis factor-alpha (TNF-α) therapy for inflammatory bowel disease. Initially, they were described as isolated events among patients who received the aforementioned drug agents for inflammatory rheumatic diseases. Later, paradoxical reactions have been reported in association with other conditions as psoriasis and inflammatory bowel disease and different biologic drugs or classes. Furthermore, paradoxical reactions have been reported with other biologics than TNF-α inhibitors, such as ustekinumab and IL-17 and IL-23 inhibitors. Sometimes, differentiating a true paradoxical reaction from a disease flare caused by efficacy loss can be challenging. The hypothesis concerning its pathophysiology consists in an imbalance of the immunity and inflammatory mechanisms and cells implied (cytokines, lymphocytes…). These reactions may hinder proper patient management and result in catastrophic consequences. Thus, close surveillance and early recognition of these drug class effects is crucial.

Keywords: *Biologics. Therapy. Psoriasis. Paradoxical.*

Introduction

Paradoxical reactions (PRs) are defined as adverse effects that manifest as a *de novo* appearance or the exacerbation of a condition that commonly responds to a certain class of biologic agent. Initially, they were described as isolated events among patients who received the aforementioned drug agents for inflammatory rheumatic diseases. Later, as more biologic agents have emerged, paradoxical reactions have been, and are being, reported with other conditions as psoriasis and inflammatory bowel disease (IBD) and with different biologic drugs or classes. Although the most reported drugs to be involved in paradoxical reactions are anti-TNF-α drugs, both IL-12/23, IL-17/17R, and IL-23 inhibitors have also been involved. In their review, Murphy et al. reported a proportion of anti-TNF-α involvement in 91.2% (1869/2049) of all cases, followed by IL-17/17R (3.5%), IL-4Rα (2.7%), IL-12/23 (2.4%), and IL-23 (0.01%) inhibitors[1].

A well-known example is the debut of psoriatic eruptions when patients with no history of psoriatic disease undergo anti-tumor necrosis factor (TNF-α) therapy for Crohn's disease or rheumatoid arthritis, or the worsening of pre-existing psoriasis when these drugs are employed for cutaneous or articular manifestations of the disease itself. Sometimes, these reactions debut as phenotypical changes such as pustular, inverse, or guttate psoriasis in patients with a history of vulgaris plaque psoriasis. Phenotypically overlapping reaction patterns are not rare[1]. Nonetheless, they may also manifest as systemic flares of the underlying condition, such as pyoderma gangrenosum and Crohn's disease[2,3].

Sometimes, differentiating a true PR from a disease flare caused by efficacy loss due to suboptimal serum levels or anti-drug antibodies can be challenging. Phenotypical

***Correspondence:**
Guillermo J. Sánchez-Rodríguez
E-mail: GSanchezR@santpau.cat

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changes, frequently associated with PR, may be helpful to differentiate these entities, although sometimes, they can take place as part of the natural development of the disease, hence the difficulty of the management of these events[2-5].

Another controversial matter is the debut of adverse effects due to cytokine dysregulation that might not be considered true PR, such as eczematous reactions or induced inflammatory bowel disease, since they are provoked by the intrinsic mechanism of action of the drug. A known example is the development of induced IBD when anti-interleukin (IL) 17 drugs are employed, given the role this interleukin professes in maintaining homeostasis of the digestive tract mucosa. Furthermore, eczematous reactions secondary to IL-17 blockade and Th2 pathway hyper-regulation have been reported as a known drug class effect (12.1% of patients in ixekizumab Phase III trial, for example)[2-5].

Paradoxical psoriasis

In 2003, the first cases of psoriasiform dermatoses triggered by an anti-TNF-α drug were reported: three patients who underwent treatment with infliximab due to ankylosing spondylitis developed palmoplantar pustular psoriasis. A year later, the first case of infliximab-induced psoriasis was described in a patient with IBD. In his previous review from 2018, Puig described and summarized several systematic reviews, case series, and pharmacovigilance reports concerning paradoxical reactions. It seems that there is a female predominance with higher rates of plaque psoriasis and palmoplantar pustular psoriasis forms, although several phenotypes have been reported (inverted, guttate, and/or erythrodermic). This high incidence of paradoxical palmoplantar pustular psoriasis is remarkable given that only 1.7% of psoriatic patients present this form in the general population. It is not still clear whether plaque or palmoplantar pustular is the most frequent form of paradoxical psoriasis. Proportion rates of 44.8% and 36.3% for plaque and palmoplantar pustular psoriasis, respectively, were reported in the review by Brown et al., contrasting with a proportion of 49% for plaque and of 52% for palmoplantar pustular in the review from Collamer et al. An estimated incidence rate of anti-TNF-α triggered psoriasiform dermatoses of 1.04-3.00/1000 person-years has also been reported in the literature, with infliximab as the most frequent anti-TNF-α involved, followed by adalimumab, making psoriatic dermatoses the most frequent form of PR and exceeding psoriasis prevalence among the general population (around 2%)[6,7]. Iborra et al. reported the prevalence of this side effect as between 1.5% and 5% in patients who were using anti-TNF-α due to IBD[4].

The management approach includes ruling out the involvement of drugs and events that might induce psoriasis, such as infections or stress, but also the development of anti-drug antibodies or low serum levels of the biologic agent. Several authors suggest that while mild paradoxical psoriasis can be managed with the association of topical agents, biologic treatment suspension and/or drug class change might be necessary when addressing more severe cases. The latter is supported by several reports of PR relapse when the involved anti-TNF-α drug or another from the same class was reintroduced, hence the indication for switching drug classes (to ustekinumab, for example)[2,6-8]. In their systematic review, Brown et al. reported resolution rates in patients who discontinued TNF-α therapy (47.7%), switched to a different TNF-α agent (36.7%), and continued the same TNF-α therapy (32.9%)[7]. They also describe paradoxical psoriasis as an early adverse event with the majority (69.9%) occur within the 1st year of treatment[7].

It is believed that the blockage of TNF-α by biologic agents may induce increased secretion of interferon-gamma (IFN-ϒ) by plasmacytoid dendritic cells since, when unaltered, it acts as a downregulating feedback loop (Fig. 1). This hyper-regulating stimulus with increased IFNϒ levels may subsequently promote lymphocytes to paradoxically produce TNF-α. Another theory holds that the blockade of TNF-α induces an activation of Th17 and downregulation of Treg, followed by production of IL-22 by Th17, resulting in activation of keratinocytes and inflammatory loop. These theories are consistent with the reports of effectively treatment of paradoxical psoriasis with ustekinumab (anti-IL 12/23), since IL-23 is the main promoter of Th17 differentiation[5,8]. Genetic polymorphism of the IL-23 receptor, CTLA-4, and FBXL19 genes has also been related to higher risk of paradoxical psoriasis[2,9]. Furthermore, increased levels of IL-36, an interleukin related to pustulosis psoriasis, have been reported in skin biopsies from patients with Crohn's disease and anti-TNF-α triggered pustular psoriasis.

Nonetheless, anti-TNF-α is not the only drug class involved in paradoxical psoriasis: debut, worsening, and phenotype changing flares have been reported with drugs from other classes such as secukinumab (anti-IL17), ustekinumab (anti-IL12/23), tocilizumab (anti-IL6), or abatacept (anti-CTLA-4 fusion protein), in the form of generalized and palmoplantar pustular psoriasis, inverse psoriasis, and/or plaque psoriasis[2,10-18].

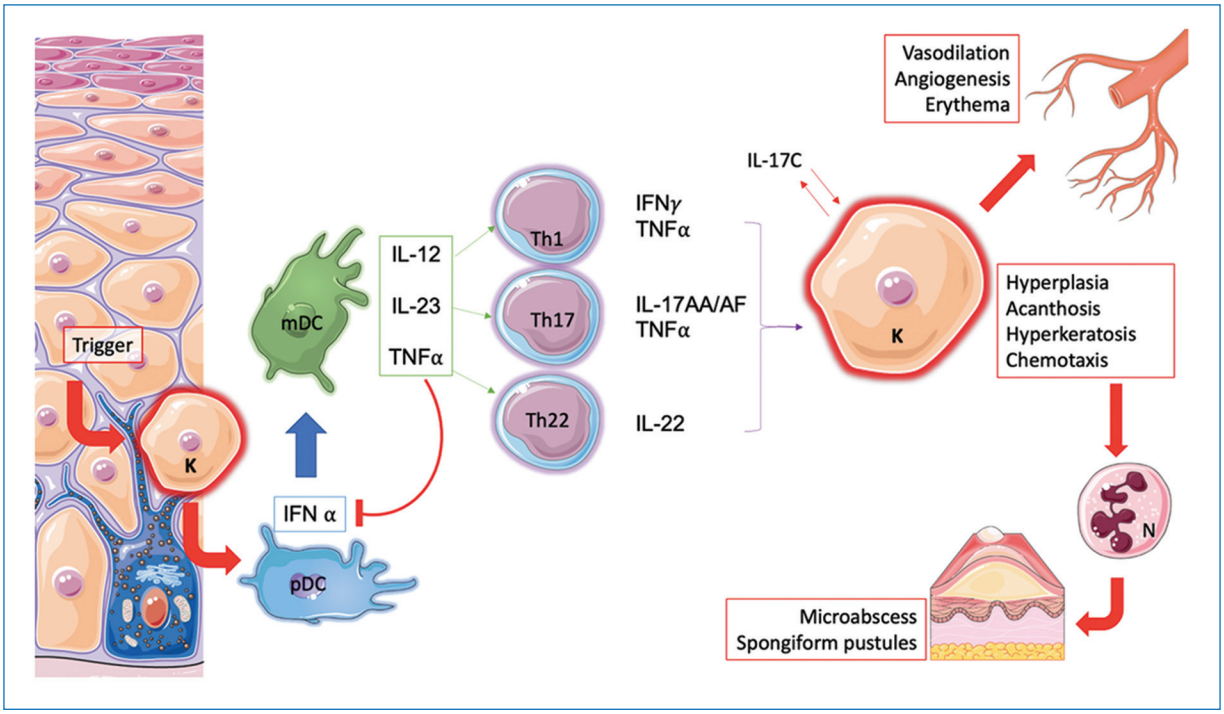

Figure 1. Simplified immunological pathways of psoriasis.
K: keratinocyte; pDC: plasmacytoid dendritic cell; mDC: myeloid dendritic cell; N: neutrophil; TNF: tumor necrosis factor; IFN: interferon.

For example, Dogra et al. reported a patient who developed generalized pustular psoriasis while undergoing secukinumab for plaque psoriasis, which was under clinical remission when the phenotype change took place. A switch to infliximab was decided with optimal response. Interleucin-17 blockade might cause compensatory overproduction of the cytokines earlier in this pathway, such as TNF-α, IL-23, and IL-12[10].

Ustekinumab has been successfully employed as a treatment for paradoxical psoriasis, mostly anti-TNF-α triggered psoriasis, but it has also been reported in literature as the culprit. Wenk et al.[13] first reported a case of paradoxical flare of psoriasis after ustekinumab injection, in which the patient experienced worsening of skin lesions whenever she was injected. Lee et al.[14] also reported the case of a 24-year-old who suffered from moderate-severe psoriasis vulgaris and underwent treatment with ustekinumab. After manifesting a dramatical initial improvement, he experienced sudden and severe worsening upon the third injection of the drug. These two examples in particular did not show any phenotypical change.

Benzaquen et al.[15], on the contrary, described the first case of palmoplantar pustular psoriatic debut on a patient who suffered from IBD with axial articular involvement. He had no previous personal history of psoriatic disease. Ustekinumab was discontinued and replaced by golimumab with excellent response.

Another specific phenotype of paradoxical psoriasis has been described in patients treated with anti-TNF-α but also anti-IL17 (ixekizumab) drugs in the form of psoriasiform alopecia, which is an infrequent and severe form of psoriasis among the general population, but remarkably higher among patients undergoing TNF-α inhibitor therapy, thus, it should prompt consideration of TNF-α inhibitor-induced psoriasis[2,7,10-12,15-17,19].

Paradoxical psoriatic arthritis

The development of paradoxical arthritis with anti-TNF-α agents and ustekinumab has also been reported by different authors[2,20,21]. Several articles describe articular flares among patients with no previous history of arthritis who underwent anti-TNF-α therapy for plaque psoriasis or IBD. Concerning ustekinumab, Stamell et al.[21] reported four patients who underwent ustekinumab monotherapy for plaque psoriasis that resulted in disabling flares of known psoriatic arthritis or unmasked previously occult joint disease. In all of

our cases, psoriasis improved dramatically with ustekinumab therapy while psoriatic arthritis flared.

Ruiz-Genao et al.[20] employed Biobadaderm, the Spanish prospective multicenter cohort registry of psoriasis patients treated with systemic drugs, and calculated an incidence of 3.3 cases per 1000 person-years of *de novo* psoriatic arthritis among patients treated with biologic therapy. Remarkably, they found no cases of *de novo* articular flares among patients treated with traditional systemic drugs. Three out of nine patients achieved articular remission with no other intervention than drug suspension. No patient experienced new flares after drug with and avoidance of the suspected culprit.

Remarkably, paradoxical worsening of rheumatoid arthritis treated with this drug class – in the form of polyarthritis–has also been described in literature, with an estimated prevalence of 2.8%[2]. Controversially, some of the reported cases of articular flares among psoriatic patients also presented skin worsening–when most on the times a PR occurs, the underlying condition stays clinically stable-stating again the difficulty to differentiate true PR from loss of effectiveness[1,3,5,6].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is an inflammatory skin disease characterized by recurrent abscesses and sinus tract formation. The tissular necrosis factor-alpha plays a crucial role in the pathophysiology of HS. In this context, anti-TNF-α agents seem to be an effective option for moderate to severe active HS, in a significant proportion of patients. Hidradenitis suppurativa is involved in both sides of PR: as the primary indication for anti-TNF-α therapy and as a PR itself[2,22,23].

At present, adalimumab is approved for this indication and is also the most frequently associated drug (48%) to paradoxical HS, but similar cases have been reported involving biologic drugs from a different class, such as ustekinumab. In these situations, the withdrawal or change of drug and the specific treatment for HS achieved its partial or complete improvement. Reintroduction of same class biologic agents should be discouraged given the risk of new paradoxical flares[2,22,23].

For instance, Faivre et al.[22] described 25 patients (15 inflammatory rheumatism, nine Crohn's disease, and one psoriasis) who developed paradoxical HS when undergoing biological therapy with adalimumab, infliximab, etanercept, rituximab, and tocilizumab. Their patients showed clinical remission or improvement when the suspected drug was stopped and switched to a different drug class.

Interestingly, in the spectrum of follicular dermatoses, acne has also been reported as an adverse reaction to biologic therapy in a report that describes acneiform flares on a patient with IBD treated with vedolizumab (an $\alpha4\beta7$ integrin inhibitor for IBD).[24]

Paradoxical inflammatory bowel disease

Inflammatory bowel disease (ulcerative colitis and Crohn's disease) has also been described by several authors as a PR to biologic therapy, with a prevalence of around 43 times higher than in the general population[1,2,4]. In the available literature, it is mostly associated with etanercept in reports concerning juvenile idiopathic arthritis and other inflammatory rheumatic conditions like ankylosing spondylitis, presenting in the form of Crohn's disease. Nonetheless, paradoxical ulcerative colitis has also been described amongst psoriatic patients treated with adalimumab. In the latter, drug class switch is recommended, preferably to one indicated for both conditions, when available, like ustekinumab[1,2,4].

Uveitis

Similarly to HS, autoinflammatory and non-infectious uveitis stand at both ends of PR as a primary indication for biologic therapy and as an adverse effect. Anti-TNF-α drugs seem to be effective in reducing the frequency and severeness of uveitis associated to ankylosing spondylitis, juvenile inflammatory arthritis, or Behçet disease. Nonetheless, according to several reports[1,2,4,25], uveitis can flare or debut during biologic therapy, being etanercept the most frequently involved drug (84%), prescribed mostly for spondyloarthropathies. Treatment had to be discontinued in a minority of cases, but the uveitis recurred when the same biologic treatment was reintroduced[1,2,4,25].

Borderline and other paradoxical reactions

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis known to be associated with IBD, especially when the disease is active. Anti-TNF-α drugs are often prescribed for IBD, achieving clinical remission in a significant proportion of patients, hence also controlling PG flares. Interestingly, PG has also been reported as a PR in patients with IBD clinically inactive who undergo anti-TNF-α therapy[2,26-28].

Some conditions, also related to inflammatory and cytokine imbalance such as granulomatous diseases,

vitiligo, alopecia areata, or vasculitis, have also been reported as *borderline* PR since they do not stand as a primary indication for anti-TNF-α biologic therapy but are known to clinically improve in a significant proportion of patients when they undergo the mentioned drugs for a different primary indication[29-33]. It is believed that TNF-α blockade upregulates IFN-ϒ production, as mentioned before, predisposing to autoimmune conditions, and even antinuclear antibodies production[2].

Several granulomatous conditions are known to improve with anti-TNF-α treatment. Granuloma formation and stabilization are one of the many roles of TNF-α. Nonetheless, paradoxical granulomatous reactions have been documented to date in the form of cutaneous and systemic sarcoidosis, granuloma annulare, and interstitial granulomatous dermatitis, in patients with inflammatory rheumatic conditions such as rheumatoid arthritis or ankylosing spondylitis, but also among IBD and psoriatic population. Etanercept is the most frequently reported drug in this context, but many other from its class have caused superimposable cases. In literature, interstitial granulomatous dermatitis has also been associated with IL-6 blockade with tocilizumab[2,30-33]. In their review, Decock et al. described 90 patients who developed sarcoidosis-like lesions while undergoing anti-TNF-α therapy. In most cases, the culprit anti-TNF-α drug was etanercept. The underlying disease was rheumatoid arthritis in most cases, followed by ankylosing spondylitis and psoriasiform arthritis. Almost 80% of the cases required drug suspension and specific therapy for the PR, presenting with clinical relapse in seven out of the 20 cases where anti-TNF-α agents were reintroduced.

Discussion

Since the introduction of biologic treatments, a wide range of paradoxical reactions has been described, especially concerning anti-TNF-α agents. Early recognition and treatment of these drug class effects is of crucial importance, especially in conditions such as IBD, where the therapeutic availability is relatively lacking alternatives and reactivation of the primary disease may have catastrophic consequences. On the contrary, skin and musculoskeletal manifestations of paradoxical reactions can cause serious handicap, and adequate knowledge of the different therapeutic alternatives is required.

In this review, many PR have been summarized, especially those concerning dermatological conditions.

Paradoxical adverse reactions surface from an immunological pathway and cytokine imbalance propitiated by the intrinsic action mechanism of the different drugs reported.

On the one hand, when anti-TNF-α agents are involved, it is believed that increased levels of IFN-ϒ are the culprit of autoinflammatory and autoimmune debuts. On the other hand, when anti-IL17 or anti-IL23 drugs are involved, as mentioned before, their blockade might cause compensatory overproduction of the cytokines earlier in this pathway (such as IL-23, IL-12, IL-22, and/or TNF-α). The pathophysiological bases of granulomatous or autoimmune paradoxical conditions remain unknown, while overproduction of IFN-α stands as the main suspected culprit.

What seems to be certain is that drug class switch may be necessary for the management of each and every kind of PR, when available.

Recognition, classification, and discerning from disease worsening are still challenging but remain a cornerstone in the management of these reactions and impairment prevention.

Conclusion

True paradoxical reactions are the ones that appear when the biological drug is used to treat the disease presented as paradoxical. A wide spectrum of paradoxical adverse effects has been and is being, described since the approval of biologic drugs. Other skin conditions that appear under biological treatment such as alopecia areata, vitiligo, interstitial granulomatous dermatitis, or acneiform reactions might be considered as side effects or borderline paradoxical reactions. The most common paradoxical reaction is paradoxical psoriasis. The management of a paradoxical reaction does not necessarily mean the withdrawal of the biological treatment, but it might be inevitable in severe cases. Paradoxical reactions often require multidisciplinary approach to select the best option of treatment in every patient. These reactions may hinder proper patient management and result in catastrophic consequences. Thus, close surveillance and early recognition of these drug class effects is crucial.

Conflicts of interest

Anna López-Ferrer has received honoraria as speaker/consultant and for participation in clinical trials with Abbvie, Amgen, Almirall, Boehringer Ingelheim, Janssen, Leo-Pharma, MSD, Novartis, Eli Lilly, and UCB Pharma.

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Ethical disclosures

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).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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