Review Article

Paradoxical Reactions to Biologicals in Chronic Inflammatory Systemic Diseases

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Summary

Background: Biological agents that contain substances affecting the immune system are increasingly being used to treat chronic inflammatory systemic diseases. Aside from the expected adverse effects, they can also induce unexpected paradoxical reactions (PR). A reaction is called paradoxical when a substance that is generally therapeutically effective induces the opposite of what is intended, with the new appearance or exacerbation of inflammatory changes in the skin and other organs.

Methods: The paradoxical reactions that have been described since 1997 are presented here on the basis of the available literature on the main types of chronic inflammatory systemic disease, which was retrieved by a selective search in the PubMed and Google Scholar databases.

Results: Many studies and registers to date contain no mention of paradoxical reactions. Anti–TNF-alpha treatment for patients with ankylosing spondylitis leads to paradoxical reactions in 19 per 1000 patient years, compared to 11 per 1000 patient years with conventional treatment; the corresponding frequency for paradoxical psoriasis in patients with other chronic inflammatory systemic diseases are 1.04–3.68 versus 1.45 per 1000 patient years. Paradoxical reactions tend to be more common with anti–TNF-alpha treatment than, for example, with the administration of ustekinumab, vedolizumab, and other agents. It is unclear whether some drugs have been noted to cause PR more commonly than others because of varying times since their approval, differences in immunogenicity, and differences between their target structures.

Conclusion: Paradoxical reactions induced by biological agents are a problem confronting physicians in multiple specialties. They need to be distinguished from infectious and neoplastic diseases and from autoimmune conditions of other types. The treatment options for paradoxical reactions include local treatment, symptomatic therapy, prednisolone administration, and the discontinuation or switching of the biological agent, although some patients will react with a further paradoxical reaction to a different biological agent that is used instead.

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The treatment of rheumatoid arthritis (RA), spondyloarthritis (SPA), chronic inflammatory bowel disease (IBD), psoriasis (PSO), and other chronic systemic inflammatory diseases has been significantly improved by the use of biological agents (biologics, biologicals). Biologics are genetically engineered, high molecular weight proteins that resemble the body's own substances. These include anti-tumor necrosis factor (TNF)-alpha monoclonal antibodies, PEGylated Fab' antibody fragments (certolizumab), TNF receptor Fc fragment fusion proteins (etanercept), cytokine antagonists (for example, interleukin (IL)-12/23 antagonist ustekinumab), receptor and integrin antibodies (for example, vedolizumab), and therapies directly targeting cells (1–3). Administered parenterally as (glyco)proteins, they can trigger the following reactions (4–6):

- non-immunological, dose-dependent immunosuppressive adverse drug reactions (ADRs)
- allergic and non-allergic hypersensitivity reactions
- unexpected paradoxical reactions (PR).

Whereas non-immunological, dose-dependent immunosuppressive ADRs of biological agents are recorded in many registers compiled by various

disciplines (1–3, 7–9, e1–e4), PR are considered rare individual immunological reactions (1–3, 10).

Definition of paradoxical reactions and clinical problems

Paradoxical reaction is the term used to describe the effect of a drug approved for a specific indication when the use of this otherwise therapeutically active substance induces the opposite of what is intended, the recurrence of non-infectious inflammation, or the exacerbation of a predisposed disease (10–13, e1–e3, e7–e9). Criteria for PR are met when there is no infection or activation of an occult infection, no biological agent-induced autoimmune reaction, and no malignant transformation, and the new-onset disease manifestation is not due to an increase in disease activity of the underlying condition (10–14, e2, e5, e6).

Since around 1997, PR became known mainly in connection with anti-TNF-alpha therapies (1–3, 10–13, e2, e3, e7). Nowadays, the spectrum is widening to include many other groups of biological agents and needs to be continually updated (13, e7, e10–e23). The main clinical problem of PR is to recognize such reactions at all, because it is not uncommon for the patient to present to a different specialty than that which initially prescribed the biological agent (12, 14–21). Being able to even consider PR when making a diagnosis requires an accurate medication and family history (predisposition).

The aim of this review article is to present the results of a literature review using the search term "paradoxical reaction to biologicals" in the PubMed and Google Scholar databases up to May 2021 and to differentiate PR from other adverse reactions. It became apparent that PR were not considered a particular problem, even in larger registers, due to their uncommon nature (1–3, 7, 10, e1–e3, e5–e8). This is also a possible reason for the lack of references to PR in drug approval studies (for example, in the benefit analysis of the German Institute for Quality and Efficiency in Health Care [IQWiG]), even after thorough evaluation (7, e1-e3), and in product information documents.

BOX

Definition and characteristics of paradoxical reactions

- Paradoxical reactions (PR) are defined as an exacerbation or new-onset of non-infectious inflammatory skin and other organ changes upon use of a substance that is in principle therapeutically effective.
  - PR are not limited to biological agents and may also occur in association with other drug groups.
  - PR are being increasingly reported in connection with biological agents, especially since the introduction of anti-TNF-alpha therapies but are not caused by a class effect of TNF-alpha inhibitors, as PR are also possible with other biological drugs.
  - One characteristic of PR is that they are often effective in inflamed tissue, while certain immune dysregulations occur in other noninflamed organ areas.
- Paradoxical reactions can
  - develop during a controlled underlying condition,
  - also occur after discontinuation of the biological agents (in contrast to other allergic or non-allergic adverse drug reactions), but also
  - may be associated with, or complicate, the underlying condition, for example as a spontaneous or induced change in disease phenotype
- Paradoxical reactions demonstrate different kinetics (several days – weeks) to
  - allergic type I-IV reactions and
  - non-allergic reactions (intolerance reactions)
- With biological therapy, before a paradoxical reaction is diagnosed, it is necessary to distinguish, among other things:
  - extraintestinal symptoms or a change in manifestation of the underlying condition
  - induction of autoimmune phenomena (biologic-induced autoimmunopathy, for example: drug-induced lupus erythematosus) or of anti-drug antibodies (ADA)
  - formation of biological/ADA immune complexes (type III allergy)
  - activation of occult infections; differential diagnosis of new infections in the presence of a known risk from immunosuppression
  - development of malignancy (for example lymphoma)

Paradoxical reactions are unexpected immunological intolerance reactions during, or after, therapy with biotechnologically produced substances (biological agents) (4, 8, 13, 15, 25, 28, 29, 40, e5–e9)

Results

PR are considered aberrant, immunologically explainable disease reactions. They may present in various organs with few manifestation clusters (for example, psoriasiform skin reactions, arthralgias, or arthritis) and in many other more uncommon manifestations (for example, granulomatous skin and lung lesions, vasculitis, pyoderma gangrenosum). PR during biological therapy show different underlying kinetics than typical adverse drug reactions. They occur after a median latency of 6–12 months of therapy, with individual cases of PSO reported as early as 4 days of treatment (1–3, 10, e1, e5). Their occurrence is difficult to predict due to the lack of biomarkers with high predictive power and no phenotypic spectrum nor clinical characteristics.

It is typical for the majority of PR that good therapeutic efficacy is usually found in the organ system presenting the inflammatory manifestation for which the therapeutic indication exists. In contrast, a new disease symptomatology is subsequently induced in other, non-involved organ systems due to an immunopathological reaction, or an established disease predisposition is exacerbated (1, 3, 10–14, 21–28). Extremely rare exacerbations and changes in disease phenotype in the affected organ system have also been reported (20, 21, 28, e2, e5, e6, e23–e25).

Characteristic features of PR found in the literature and those based on our own experience are listed in the *Box*. PR are not a class effect of anti-TNF-alpha therapies, because they also occur in association with other biological agents (for example, IL-17

TABLE 1

Overview of common paradoxical reactions occurring during treatment with biological agents for chronic systemic inflammatory diseases

Substance	Cohort	Induced PR	Population treated with biologics: Incidence of disease manifestation per 1000 person-years	Conventionally treated population: Incidence of disease manifestation per 1000 person-years	References
TNF inhibitors					
IFX, ADAL, ETN	AS	several PR	19	11	(e51)
ADAL = ETN >> IFX	AS	enterocolitis	23/22/2	13	(28, e64)
ETN >> ADAL, IFX	JIA	enterocolitis	3.62	–	(33, 38, e58)
ADAL >> IFX >> ETN	RA	psoriasis	1.04–3.0	0	(16,17)
	RA	psoriasis	2.31	–	(e52)
	IBD	psoriasis	3.68	1.45	(20)
	IBD	arthralgia/arthritis	20.5	–	(19)
Other biologics					
Tocilizumab	RA	several PR	2.62	–	(e59)
Anti-IL12/IL23	IBD	arthralgia/arthritis	9–193	–	(e72)
Anti-IL17	PSA, AS	enterocolitis	2.4	–	(13, e65)
Anti-IL17	AS	enterocolitis	2.0–8.0	–	(13, e70)
Rituximab	RA	psoriasis	1.82	–	(28, e57)
Vedolizumab	IBD	arthralgia/arthritis	115.6	–	(e77)
		psoriasis	47.6	–	

It is only possible to show the incidence of certain therapy-induced PR based on the results of a few studies. The incidence depends, among other things, on geographic, genetic and patient-related factors, how often biological agents were used, as well as on the underlying condition and the observation period. Although the development of arthralgias/arthritis after ustekinumab and vedolizumab has been reported, it has not been consistently classified as a PR (e63, e72–e77). Enterocolitis includes forms similar to Crohn's disease (ileitis, ileocolitis, etc.) or ulcerative colitis (colitis, proctitis) (13, 21, 28, 32, e23–e25, e27, e28).

ADAL, adalimumab; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; ETN, etanercept; IFX, infliximab; IL, interleukin; JIA, juvenile idiopathic arthritis; PR, paradoxical reactions; PSA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor; >>, qualitatively more common than ...

antagonists, ustekinumab, tocilizumab, etc.) (7, 10, 13, 21, 22, 26–29, e26).

Incidence rates of paradoxical reactions to biological agents

Incidence rates depend on the examined patient population, the biological agent used, duration of treatment, study or observation period, concomitant immunosuppression, and the question of whether the reaction is even recognized as a PR (3, 10–19, e5–e7, e10). Based on literature data, different rates are found among anti-TNF biologics, for example, for how often PSO occurs in RA or in Crohn's disease and ulcerative colitis, or uveitis and enterocolitis in rheumatic diseases, including juvenile idiopathic arthritis (JIA) (16, 17, 20, e51–e54, e60–e64). The question of whether a PR occurs at all and preferentially in a certain patient population, and in what form or frequency depends not only on the biological agent, but also on patient-specific factors (*Table 1*; 10–19, e23–25, e60–64). As yet, there are no comprehensive systematic surveys covering all indications and groups of biological agents (13, 21, e19–25). The evaluation of incidence rates is largely limited by the fact that longer prescription periods, a larger number of indications, and thus higher prescription numbers are available for anti-TNF drugs than for newer biologics (for example, ustekinumab, vedolizumab) (21, 26, e27, e69, e43, e72–e77). This could lead to PR being underestimated for future biological agents, so this should be taken into account when interpreting *Table 1*.

That PR do exist is confirmed by the evaluation of conventionally treated control collectives in which either no or very few PR were detected (16, 17, 20, e51, e60–e64).

For example, in the product information documents of TNF inhibitors, infusion reactions are reported as very common (>1 : 10 for infliximab) and PSO lesions, rash, urticaria, alopecia, and eczema, etc., as common (1 : 10–1 : 100), although PR are not explicitly mentioned and no differentiation is made between paradoxical and allergic adverse reactions (e12–e16).

The spectrum of important PR known to date is listed in *Table 2*. Apart from typical reported PR, such as PSO, arthralgias, or arthritis, many uncommon individual forms have been also been described (3, 12–14, 16, 21–23, e1–e3, e11, e16–e25).

TABLE 2

Semiquantitative spectrum of paradoxical reactions (PR) to biological therapy in chronic inflammatory systemic diseases

	Etanercept	Infliximab	Adalimumab	Certolizumab Golimumab	Ustekinumab	Secukinumab Ixekinumab Brodalumab	Rituximab	Tocilizumab
Alopecia	++	++	++	+	-	-	-	-
Arthritis*[1] and arthralgias	+++	+++	+++	-	++	-	-	-
Acne inversa/Hidradenitis suppurativa*[2]	+	+	++	-	+	-	(+)	-
Chronic bowel inflammation*[3]	++	+	+	(+)	-	++	-	-
Eczema, cutaneous vasculitis	++	++	+	(+)	-	(+)	-	(+)
Lichen ruber, planopilaris and similar forms	-	-	+	-	-	-	+	-
Lupus-like syndrome	+	+++	++	-	-	(+)	(+)	(+)
Myositis	+	-	-	-	-	-	-	-
Neurological manifestations	+	-	-	-	-	-	-	-
Psoriasiform skin reactions	+++	+++	+++	++	++	++	+	(+)
Sarcoidosis and similar granulomatous organ and skin reactions	+++	++	++	+	-	-	+	(+)
Uveitis	++	+	+	-	-	-	-	(+)
Uncommon reactions*[4]	(+)*[5]	(+)	(+)	(+)	(+)	(+)	(+)	(+)*[6]

Presentation of the paradoxical reactions found in the literature, classified according to incidence rates and based on published patient reports. Since the individual biological agents are prescribed for different periods of time, have various indications, and are not similarly distributed, the incidence rates are not entirely comparable. The table does not claim to be complete, as ongoing updates are necessary due to the growing range of available treatments using biological agents (3, 13, 32, 33, 36, 40, e11, e16, e19, e36, e40–50, e56–e57, e63, e69–e77). Apart from arthralgias/arthritis and psoriatic skin florescences, no PRs as such have so far been reported for vedolizumab (35, e27, e45, e63, e76–e77).

+++, > 100 patients; ++, >10 patients, +, 3–10 patients; (+), 1–2 reported patients

*[1] including juvenile idiopathic arthritis (JIA),

*[2] acne inversa/hidradenitis suppurativa, *[3] chronic intestinal inflammation (colitis and/or ileitis) (32, 33, e23–e25).

*[4] Note other "rarest paradoxical reactions" that include *[5] bronchial asthma after etanercept,

*[6] cutaneous sarcoidosis after tocilizumab or exacerbation of atopic dermatitis from ustekinumab and etanercept, bullous dermatoses, granuloma annulare, osteonecrosis, synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO), Sweet's syndrome, pyoderma gangrenosum after certolizumab, and thrombotic thrombocytopenic purpura, vitiligo, etc., after golimumab(13, 14, 21, 22, 31, 37–40, e2, e6, e11, e16, e22, e28–e31, e36, e40–e50, e56–e57, e63, e69).

Immunopathogenesis and differential diagnosis of paradoxical reactions in chronic inflammatory systemic diseases

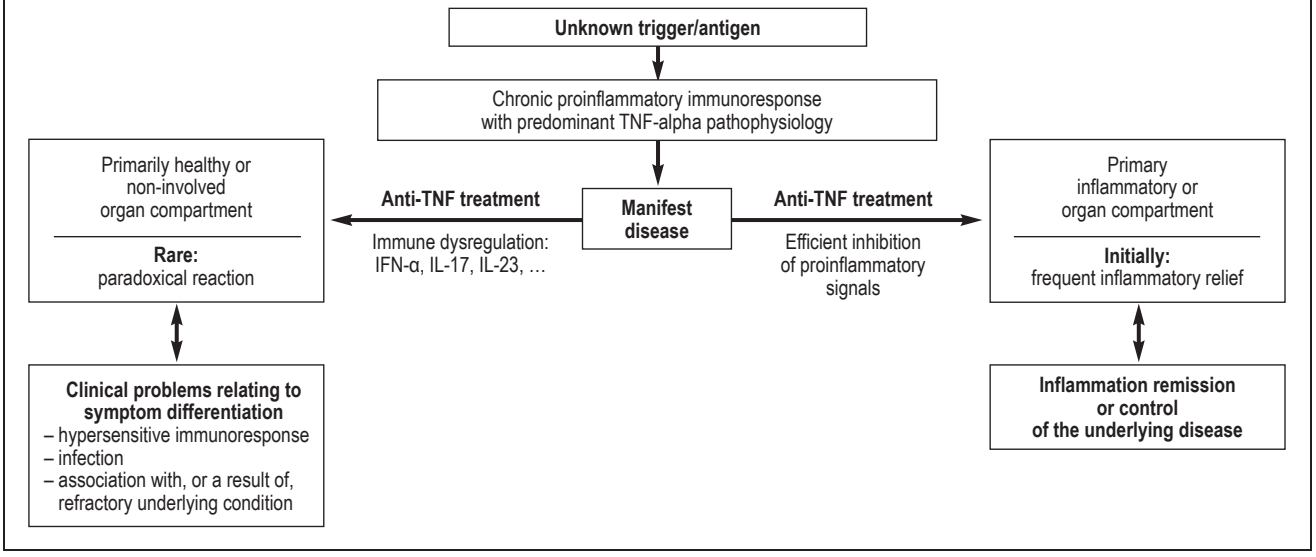
Suspected PR must be distinguished from an infectious complication, change in disease phenotype, and extra-intestinal manifestations (for example, an eye inflammation concomitant to IBD). A PR may also present as a significant deterioration of the underlying condition, change in clinical picture (for example, change from plaque PSO to pustular PSO), a new-onset of another disease, or a relapse (7, 10–21). Systemic symptoms such as fever, lymphadenopathy, skin and eye lesions, as well as hepatosplenomegaly, in addition to sarcoidosis-like lung and skin changes, should in the first instance suggest infection, tuberculosis or lymphoma development. They should therefore first be excluded during biological therapy (7, 10, 14, 16, 20–23) before the above criteria for PR are considered to be fulfilled (*Box*; 7, 10, 14, 16–23).

New disease symptoms must be distinguished from deterioration of the underlying condition (review the disease activity) or loss of efficacy of the biological agent. For example, secondary loss of effect of the biological agent can develop if the drug is excreted secondary to protein-losing enteropathy, or if antibodies (also known as anti-drug antibodies [ADA]) are formed (1, 11, 18). If the clinical picture is unclear, the therapeutic levels of the biologic used or, with certain substances, the ADA may be measured to detect loss of active substance or a reduced effect due to antibody formation (1, 11, 17–21, 24, 25). With PR, the plasma levels of the biologics are usually within normal limits.

The problem is that in some patients the development of PR during biological agent use is varied and unpredictable. Even after a biological agent has been withdrawn or a switch to a biologic of a different class has been made, PR may still recur in genetically predisposed patients (10, 16, 17, e2, e4, e8, e11, e16). In the literature, even double and triple PR have been reported in individual patients (16, 17, 19–21).

A model explaining the majority of PR to TNF inhibitors is shown in the *Figure*. Not only can a biological agent reach the inflamed organ compartment, where it exerts its anti-inflammatory effect, but it also

FIGURE



Immunopathogenetic explanatory model illustrating the emergence of paradoxical reactions using TNF-inhibiting biological agents

The development of a paradoxical reaction in an organ compartment not primarily affected by the inflammatory systemic disease can be explained by various mechanisms (dysregulation of T cells, antigen or autoantigen presentation, formation of interferon-alpha, cytokine imbalance, etc.) (3, 7, 12, 13, 21, 27, 28, e2, e5, e21). The resulting new-onset or exacerbated disease symptoms often require an extensive interdisciplinary differential diagnostic workup (*Box*). IL, interleukin; IFN, interferon; TNF, tumor necrosis factor

reaches healthy tissue, where it binds to target proteins, such as TNF-alpha, alters the cytokine balance (for example the ratio between interferon and TNF-alpha), activates dendritic cells, and can thus induce the PR (1–3, 11, 16, 21, 23–26). The fact that biological agents often cause PSO lesions is due to the anti-TNF-alpha effect on the dendritic cells of the skin disinhibiting interferon-alpha formation and thereby triggering an excess production of IL-23. This ultimately causes hyperproliferation of skin epithelium by activating neutrophils via Th17 cells, on the one hand, and by enhancing IL-22 action on keratinocytes on the other (3, 17, 20, 25–27, e2, e5, e6). Similar immune mechanisms have also been reported for PR in other organ areas and, very rarely, in the inflamed organ system itself (progression of the underlying condition or primary failure of action) (12–15, 20–29, 32; e6, e18, e23, e24).

The plasticity of PR suggests diverse aberrant immune pathways. Various immune phenomena can develop, depending on the biologic used. This means, on the one hand, that PR to anti-TNF-alpha antagonists (arthritis, PSO), for example, can be treated with ustekinumab, while PR induced by ustekinumab (for example, also arthritis or PSO), on the other hand, are treatable with TNF alpha antagonists (19, 21, 26–29, e25).

Discussion and recommended action

Paradoxical reactions in dermatology

Many rare PR to various biologicals manifest frequently on the skin (*Table 2*) (3, 11–13, 16, 21, e2, e5–e7, e19, e20, e50–e57, e77).

Pustular PSO is relatively common after the administration of TNF inhibitors for the treatment of plaque PSO. In this case, the plaques can either completely transform into pustular PSO (generalized or localized) or the pustules occur concomitantly (PSO cum pustulatione) (3, 12, 21, 26, e19, e20), which usually does not happen in a spontaneous setting. The exacerbation of plaque PSO as a diagnostic indicator and even the development of PSO arthritis in patients taking biological agents are also considered PR in principle.

In rheumatology, psoriasiform (PSO-like) eczematous skin changes are relatively common in patients taking TNF blockers, as well as those on IL-6 inhibitors (2, 3, 15, 16, e63, e67). Psoriasiform skin changes are particularly evident with anti-TNF treatment of IBD patients at 3.6/1000 – as opposed to 1.4/1000 person-years with conventional treatment, with patients with Crohn's disease being more commonly affected (*Table 1*; 10–12, 17–21, e2, e5, e21, e71). Although PR are not reported in all reference citations, individual studies report of PSO-like skin changes with clinically and histologically classic PSO manifestations being induced in 3–16% of all treated patients with IBD who previously had healthy skin, (17–21, 28, e61, e63, e66, e71).

Whether a switch to IL-17 or IL-12/23 inhibitors is indicated in the event of psoriasiform skin changes in patients on TNF inhibitors has not yet been systematically investigated, but there are case reports of switching to ustekinumab after the development of psoriasiform changes (12, 26–29). Ustekinumab has

been used very effectively in patients with IBD suffering from anti-TNF-induced PSO (27). On the other hand, PR in the form of enterocolitis have also been reported to have developed in patients taking IL-17 inhibitors and ustekinumab for the treatment of PSO, PSO-arthritis and SPA (13, 21, 26–31).

There are also reports of other rare dermatological symptoms (for example, pyoderma gangrenosum, erythema nodosum, hidradenitis suppurativa) developing under biological therapy that show the typical characteristics of a PR (*Box*, *Table 2*; 21, 29–34, e6, e23, e54).

Paradoxical reactions in gastroenterology

Apart from PSO-like skin changes, arthritis and arthralgias, patients with IBD can also develop uveitis, scleritis, sarcoidosis, and pyoderma gangrenosum, among others, albeit less commonly (*Table 1*, *Table 2*). They must be distinguished from extra-intestinal manifestations and other causes.

A severe form of PR is the manifestation of enterocolitis during treatment with biological drugs. This is very similar to IBD, although not identical. It is another example of drug-induced bowel inflammation (13, 21, 26–29, 31–32). At least 158 cases of new-onset enterocolitis have been reported in the RA and JIA registers of the U.S. FDA, the majority during treatment with etanercept (82%); and more recently, some in connection with IL-17A inhibitors too (13, 21, 32, 33, 38, e18, e22, e23, e25, e58, e60, e65, e70). Basically, it also applies for IBD that a new relapse can be triggered instead of therapy-induced remission (26, 29, 31–34, e22–e25). However, in the majority of these bowel inflammations, the relapse can be successfully treated by drug withdrawal or switching to another anti-TNF antibody or to ustekinumab or vedolizumab, in addition to conventional therapy for IBD (13, 27–29, 34–36, e22–e27).

Paradoxical reactions in rheumatology

Biological agents are prescribed above all for severe exacerbations, in combination with methotrexate in RA and almost exclusively as monotherapy in SPA (2, 7, 16, 36–38, e1, e8, e28–e37).

PR have been reported in all indications and for almost all classes of biological agents across their entire range (*Table 2*) (1–3, 10–12, 16, 28, 36, e28–e30). Given their long period of availability following early marketing approval, etanercept, infliximab, and adalimumab have more comprehensive data available on PR in patients with RA, SPA, and PSO arthritis, as well as on their respective treatments (16, 36–38, e1, e8, e28–e37). In general, different immunophenomena due to TNF inhibitors are seen in patients with seropositive RA than in those with spondyloarthritis. The latter patients show more similarities with CED and PSO patients, with clustered occurrence of uveitis as well as actual CED and PSO, whereas in RA humoral immunoreactions, such as autoantibody formation, lupus-like diseases or vasculitis, are significantly more frequent (37–40, e29–e37).

The autoimmune phenomena observed in RA patients on TNF inhibitors often regress once therapy is interrupted (2, 16, 22, 36–39, e1, e8, e33, e34). Therapeutically, rituximab is especially indicated for patients presenting a humoral immunoresponse, although tocilizumab, anakinra, or a Janus kinase (JAK) inhibitors may also be used (39–40). Concomitant methotrexate therapy may reduce PR induced by biologics (19). Any known risk for autoimmune phenomena should be taken into account when selecting a biological agent. For example, etanercept and TNF antibodies should not be chosen after a history of uveitis associated with familial multiple sclerosis (36–39, e35–e40).

Treatment options for paradoxical reactions

Whether extension or change of therapy is indicated will depend on the underlying condition, the type, severity, and extent of the PR, and the therapeutic alternatives.

In the event of life-threatening or organ-threatening reactions, such as lupus-like glomerulonephritis or encephalitis, biological therapy must be discontinued and steroid therapy started at 1–2 mg/kg. Most patients respond well to this approach, so any stronger immunosuppression (e.g. with cyclophosphamide) can be avoided (2, 10–13, 21–24, 26–30, e1, e10, e16–e18, e28–e30). With life-threatening PR, the patient should not, if possible, be re-exposed or switched to an agent of the same class (for example, switching from infliximab to adalimumab) (2, 10–12, 21–24, 29). However, re-exposure or a switch may well be considered for mild and moderate forms (16–19, 21, 40, e1, e10, e23–e26).

With severe PR, the biological agent should be withdrawn (if the underlying disease is in remission) or therapy should be switched to a different class of agents (if the underlying condition is active), for example in the case of SPA treatment, from a TNF inhibitor to an IL-17 inhibitor (3, 19–21, 26, 28).

Mild to moderate PR in patients receiving TNF antagonists can often be successfully treated by discontinuing them or switching to another TNF inhibitor, ustekinumab, or IL-17A antagonist (1–3, 21–23, 26, 29, e16, e18, e20, e23). Switching to a different TNF inhibitor carries a certain risk of recurrence, depending on the clinical picture (for example, 50–60% in patients with PSO) (10, 13, 15–17, 21, 28, e18, e53, e57, e64).

Mild PR (unremarkable PSO, arthritis) can often be adequately controlled symptomatically (external medicines, non-steroidal anti-inflammatory drugs (NSAIDs), joint injections), and in pustular PSO also with the help of retinoids or by adding methotrexate. The biological agent can then be continued (2, 17–19, 21, 40).

Patients who have a paradoxical reaction to biologics should be treated, where indicated, with

conventional drugs (for example, steroids) or by applying therapeutic principles that do not induce PR (Janus kinase inhibitors) (10–12, 13, 21, 29, 35, 40, e1, e2, e24).

Conclusions

PR should be explicitly recorded in biologic registers. We advise reporting possible PR as adverse drug reactions, not least to provide a better basis for estimating incidence rates in real-world care settings.

In addition, samples from affected patients should be preserved in a biobank to identify possible genetic predisposition patterns by cluster analysis and to provide individualized treatment options in the future to avoid PR (18, 25, 36, e35, e65, e68).

Conflict of interest statement

University Lecturer Dr. Sander received consultancy payments from Swedish Orphan Biovitrium and EUSA Pharma. He received lecture fees from AbbVie, Janssen Cilag and EUSA Pharma. He served as a paid expert consultant for Hogan Lovells International LLP in a matter related to the topic.

Prof. Sticherling received research support from Novartis Pharma. He has been reimbursed for presentations by Abbvie, Almirall, Boehringer, Celgene, Janssen Cilag, Pfizer, Novartis, Leo, Sanofi and UCB. He received reimbursement of congress attendance fees and travel costs from Abbvie, Janssen Cilag, Novartis and UCB. He is a member of the Advisory Boards of Abbvie, Amgen, Biogen, Celgene, Janssen Cilag, Leo, Lilly, Pfizer, Novartis, Sanofi and UCB. He is also a member of the Scientific Advisory Board of the German Psoriasis Association.

Prof. Raithel received lecture fees from Janssen Cilag and the Falk Foundation.

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▶ **Supplementary material**

eReferences:
www.aerzteblatt-international.de/m2022.0067

CLINICAL SNAPSHOT

A Rare Case of Barotrauma Caused by Coughing

A 63-year-old man had a coughing fit and felt a tearing sensation in the right hemithorax. Clinical examination showed thoracic instability with attenuated breath sounds and extensive soft tissue hematoma. The patient's dyspnea worsened and he was transferred to Tübingen University Hospital for surgery. External trauma could be ruled out. Computed tomography showed a rupture of the muscular and bony chest wall accompanied by diaphragmatic hernia, with intrusion of bowel into the thorax *(Figure)*. Emergency median laparotomy was carried out, and the intraoperative findings confirmed the combined rupture of the diaphragm and the chest wall. After repositioning of the herniated bowel, the diaphragm was repaired with two rows of sutures. This stabilized the chest wall. After a suture was dislodged by coughing on postoperative day 5, the diaphragm was reconstructed using a GoreTex patch. The patient swiftly recovered from surgery. The cause of the cough remained unidentified. Diaphragmatic rupture caused by coughing is rare, particularly in this location with accompanying rib fractures. This case represents an example of barotraumatic injury caused by an apparently minor event.

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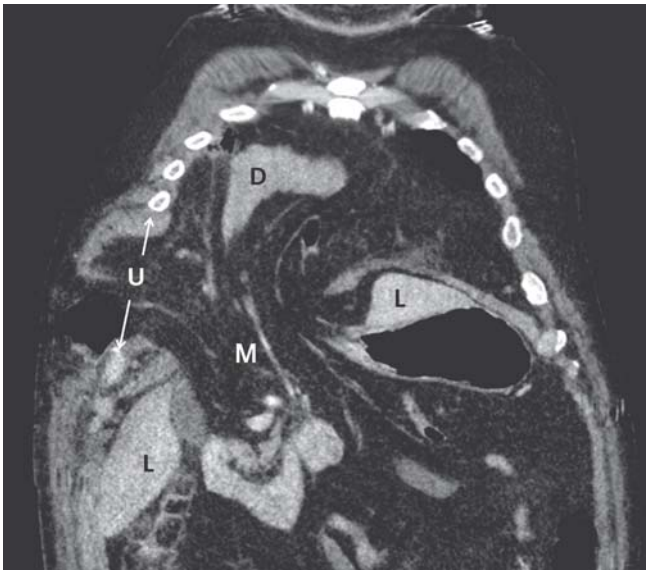
Translated from the original German by David Roseveare.



Coronal computed tomography of the thorax and abdomen shows, ventral to the liver (L), a portion of bowel (D) with mesentery (M) herniating through the diaphragm. The chest wall is ruptured between the sixth and seventh ribs (U). The diaphragm showed a long tear at the pars costalis in the right ventrolateral thorax, close to its attachment to the chest wall, with fractures of the sixth and seventh ribs.

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Questions on the article in issue 6/2022:

Paradoxical Reactions to Biologicals in Chronic Inflammatory Systemic Diseases

cme plus

The submission deadline is 10. February 2023. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

What is the mean latency reported for the occurrence of paradoxical reactions during biological therapy?

a) 6–12 hours after starting treatment
b) 6–12 days after starting treatment
c) 6–12 weeks after starting treatment
d) 6–12 months after starting treatment
e) 6–12 years after starting treatment

Question 2

To what pathomechanism is the triggering of psoriatic lesions under anti-TNF-alpha activity attributed?

a) To an increase in the production of histamine
b) To an increase in the production of IL-23
c) To an inhibition of interferon-alpha formation by dendritic cells
d) To antibody formation against anti-TNF-alpha
e) To a reduction of the effect of IL-22 on keratinocytes

Question 3

Which drug has been effectively used to treat anti-TNF-induced psoriasis in patients with inflammatory bowel disease?

a) Adalimumab
b) Infliximab
c) Ustekinumab
d) Etanercept
e) Rituximab

Question 4

Why should the assessment of the incidence rates of paradoxical reactions be interpreted with particular caution?

a) Because most prescriptions to date have been for anti-TNF drugs
b) Because there are particularly large prescription numbers for ustekinumab
c) Because there are particularly large prescription numbers for vedolizumab
d) Because paradoxical reactions due to anti-TNF drugs are difficult to detect
e) Because paradoxical reactions due to biological agents are difficult to detect

Question 5

According to literature reports, which of the following drugs is most likely to cause alopecia as a paradoxical reaction?

a) Rituximab
b) Tocolozimab
c) Secukinumab
d) Ustekinumab
e) Infliximab

Question 6

What is the explanation for the development of paradoxical reactions to biological agents?

a) Only biological agents can produce a paradoxical reaction
b) Biological agents are produced by biotechnology and can therefore have an immunogenic effect and induce anti-drug antibodies
c) Paradoxical reactions occur more frequently in patients treated with biological agents than in conventionally treated patient populations
d) Steroids are often discontinued during biological therapy
e) Chronic systemic inflammations are often associated with allergic immunoresponses

Question 7

What is the first line of action indicated when encephalitis develops during biological therapy?

a) Change treatment to use a biological agent of a different class
b) Start strong immunosuppression with cyclophosphamide immediately
c) Continue the biological therapy and commence steroid therapy (5 mg/kg)
d) Change treatment to use a biological agent of the same class and commence steroid therapy (1–2 mg/kg)
e) Stop biological therapy and commence steroid therapy (1–2 mg/kg)

Question 8

What is the incidence rate of a paradoxical reaction when treating ankylosing spondylitis with anti-TNF-alpha therapy?

a) Approx. 11/1000 person-years
b) Approx. 19/1000 person-years
c) Approx. 1.9/1000 person-years
d) Approx. 33/1000 person-years
e) Approx. 5.3/1000 person-years

Question 9

Which organ system is commonly affected in paradoxical reactions to various biological agents?

a) The brain
b) Striated muscles
c) The skin
d) The liver
e) The lungs

Question 10

To which of the following groups of biological agents does the drug vedolizumab belong?

a) Anti-TNF-alpha antibodies
b) PEGylated antibody FAB' fragments
c) TNF receptor Fc fragment fusion proteins
d) Receptor and integrin antibodies
e) Cytokine antagonists

Supplementary material for:

Paradoxical Reactions to Biologicals in Chronic Inflammatory Systemic Diseases

by Igor Kremenevski, Oliver Sander, Michael Sticherling, and Martin Raithel

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