



Hematologic side effects of biologics and kinase inhibitors used in rheumatologic diseases: a review of the current evidence

Sambhawana Bhandari¹ · Maun Ranjan Baral¹ · Matthew Barber¹ · Alla Rudinskaya² · Oleg Sostin³

Received: 27 March 2022 / Accepted: 13 June 2022 / Published online: 27 June 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Treatment options for various rheumatologic diseases have been limited until the introduction of biologic agents and kinase inhibitor therapy in recent decades. Since their arrival, they have steadily been integrated into routine management. Given their wide use and overall successful outcomes, it becomes increasingly pertinent for clinicians to readily identify their side effects. Their effects can involve multiple organ systems, including hematologic. This review aims to identify and classify the range of hematologic effects associated with individual biologics and kinase inhibitors used for treatment of rheumatologic diseases.

Keywords Hematologic side effects · Biologics · Cytokine inhibitors · Kinase inhibitors · Co-stimulation blockers

Introduction

Biologics are therapeutic agents made using recombinant DNA techniques [1]. They are divided into different classes based on their mechanism of action: B-cell depletion and inhibition, cytokine inhibition (specifically targeting TNF, IL-1, IL-6, IL-12/23, and IL-17), and co-stimulation blockers. Kinase inhibitors (KI's) are small molecules that target pathways which mediate receptor signal transduction and are not considered biologics [1, 2]. The advent of biologics and KI's has provided novel approaches to the management of various rheumatologic diseases. However, like any other therapeutic agents, they have their own share of side effects. Among the spectrum of multisystem side effects, hematological side effects should not be ignored, as they can be life-threatening. This review will focus on the current evidence and literature regarding the hematologic side effects of these agents to better identify and categorize them for clinical reference.

Tumor necrosis factor inhibitors

Five TNF inhibitors are currently available for treatment of various rheumatologic conditions: infliximab, etanercept, adalimumab, certolizumab, and golimumab. Their efficacy, safety, and tolerance have been well established [1, 3]. However, a number of hematologic side effects have been reported in literature.

Neutropenia Neutropenia is the most commonly reported hematological complication associated with anti-TNF agents; among which, etanercept has shown the highest rates [4]. Sebastian et al. reported neutropenia with infliximab use, associated with the presence of granulocyte-specific IgM antibodies that improved after drug discontinuation, and recurred after initiation of another anti-TNF agent: adalimumab, suggesting autoimmune-mediated peripheral destruction as a possible cause of anti-TNF agent-induced neutropenia. They also reported an association between previous history of neutropenia with azathioprine and mercaptopurine, suggesting history of neutropenia with other disease-modifying antirheumatic drugs (DMARDs) as a predisposing/predictive factor for neutropenia [5]. Favalli et al. further supported the autoimmune pathophysiology for neutropenia by demonstrating causality with recurrence of neutropenia to rechallenge [6]. A review article by Shivaji et al. further strengthened the association of previous history of neutropenia as a predictive factor for neutropenia, and

✉ Sambhawana Bhandari
bhandarisambhawana@gmail.com

¹ Department of Medicine, Danbury Hospital-Nuvance Health, Danbury, CT, USA

² Department of Rheumatology, Danbury Hospital-Nuvance Health, Danbury, CT, USA

³ Department of Research, Danbury Hospital-Nuvance Health, Danbury, CT, USA

added that a low baseline neutrophil count would be associated with a higher risk. They recommended that all patients receiving anti-TNF therapy have a baseline complete blood count with repeat testing every 3–6 months [7]. Datta et al. suggested maturation arrest of granulocytic cells as a possible mechanism of bone marrow toxicity from etanercept therapy [8]. It has also been postulated that neutropenia may be driven by T-large granular lymphocyte expansion through a Fas/Fas ligand interaction [9]. This effect was studied in patients undergoing treatment with adalimumab. Feuerstein et al. described several possible mechanisms of TNF inhibitors leading to neutropenia which include antigranulocyte antibody formation, increased peripheral consumption, direct bone marrow suppression, or suppression of neutrophil precursors. According to their research, treatment of persistent neutropenia and drug discontinuation is rarely necessary [4]. A study performed by Haroon et al. strongly supported this theory by showing that patients who had developed neutropenia with etanercept therapy were rechallenged with recurrence but without an increase in the risk of infections [10].

Summary

- Anti-TNF agents might be continued with caution and regular monitoring of complete and differential blood counts in case of anti-TNF induced neutropenia.
- Among other mechanisms, autoimmune-related neutropenia is the most frequently reported and discussed so far.
- Although anti-TNF agent-induced neutropenia is a known side effect, other causes of neutropenia should always be ruled out first.

Anemia This is another commonly reported hematologic complication of anti-TNF therapy. Similarly to neutropenia, there have been various mechanisms postulated and reported. Falsetti et al. described a case of adalimumab-induced thrombocytopenic microangiopathy (first dose given 15 days prior to presentation), following which the drug was promptly discontinued and plasma exchange was performed. There were no further relapses in the following 3 months. This case highlighted a possible toxic/immune-mediated mechanism associated with anti-TNF therapy leading to anemia [11]. It has been postulated that biologics can induce immune dysregulation leading to ADAMTS13 autoantibody formation causing thrombotic thrombocytopenia purpura (TTP) [12]. Similar to this, Baysal et al. described a case of thrombotic microangiopathy thought to be secondary to certolizumab, which resolved after plasma exchange and discontinuation of the drug, without any relapses [13]. Additionally, there have been case reports describing a potential association of autoimmune hemolytic anemia (AIHA) with

adalimumab therapy [14]. Harada et al. reported a case of AIHA 3 years after treatment with adalimumab, suggesting an association with long-term use [14].

Summary

- Thrombotic microangiopathies are emergent conditions which require prompt discontinuation of the drug and, in some cases, plasma exchange.
- These effects may present a few months to years after starting biologics. Thus, early recognition would be of utmost importance.
- Among patients on biologics who present with anemia, TTP should likely be considered in the differentials.

Thrombocytopenia The association of anti-TNF therapy with thrombocytopenia is thought to be much rarer in comparison to neutropenia [4]. Bessisow et al. reported 19 cases of thrombocytopenia related mainly to infliximab; among which, none was associated with any serious complications [3]. This side effect has been observed to be dose-dependent as described by Nakahara et al. [15]. Casanova et al. described adalimumab-induced thrombocytopenia with proven causality (recurrence with rechallenge) that was managed with Ustekinumab with good results [16].

The pathogenesis of thrombocytopenia as a side effect of anti-TNF therapy remains unclear, but there are several theories to its etiology. It has been considered that it may stem from the development of antiplatelet antibodies, accelerated platelet destruction, or direct bone marrow suppression [4, 7]. Boiten et al. described a case of adalimumab-induced platelet antibodies resulting in severe thrombocytopenia in a patient with Crohn's disease. Autoantibodies specific to glycoprotein IIb/IIIa and glycoprotein V platelet receptors were positive. Platelet counts showed improvement in 6 days of adalimumab discontinuation and normalized by 4 weeks [17]. Casanova et al. proposed that TNF alpha inhibitors could lead to apoptosis of Th1 lymphocytes causing an excess of Th2, which in turn may provoke antiplatelet antibody production and thus platelet destruction and thrombocytopenia [16]. Hamaguchi et al. described appearance of IgM anti-cardiolipin antibody after treatment with infliximab associated with thrombocytopenia suggesting a likely immune complex mediated mechanism [18].

A retrospective observational study by Brunasso et al. mentions thrombocytopenia with symptoms (gingival bleeding, ecchymosis, purpura, petechiae) in 4 out of 67 patients treated with either etanercept, infliximab, or adalimumab with onset of symptoms occurring at approximately 30 weeks (one patient was an outlier who demonstrated symptoms as early as nine weeks). Among the groups studied, two patients were positive for platelet surface-associated

IgG antibodies. Causality was proven with recurrence on challenge. The thrombocytopenia was treated by either drug discontinuation or steroid therapy. In one instance, there was no improvement despite these measures which was felt to be unusual given the typically transient nature of thrombocytopenia. Recurrence was also seen while switching between the infliximab to etanercept [19].

Summary

- In most circumstances, thrombocytopenia resolved spontaneously after withdrawal of the drug. However, there have been reported instances of refractory thrombocytopenia following anti-TNF use despite drug discontinuation, steroids, and intravenous immunoglobulin therapy.
- Since the mechanism is unclear and can be irreversible, regular monitoring of blood counts might be necessary. The use of another TNF agent should probably be done with utmost caution.
- Pathare et al., however, suggested that thrombocytopenia with anti-TNF agents are idiosyncratic reactions and not a class effect, and that commencing an alternative anti-TNF agent is safe [20]. They described a successful switch from etanercept to adalimumab, and infliximab to etanercept.

Eosinophilia Several case reports described eosinophilia as a possible side effect of anti-TNF alpha therapy [21, 22]. Nadeem et al. reported a case of chronic eosinophilic pneumonia with infliximab therapy, 3 months after infliximab discontinuation with persistently elevated infliximab antibodies [23]. Other reported systemic manifestations included the following: Wells syndrome and fatal acute necrotizing eosinophilic myocarditis with adalimumab [24, 25]. The mechanism discussed in these studies is the anti-TNF-induced immune deviation from Th1 to Th2 phenotype resulting in eosinophilia. More sustained TNF inhibition was associated with increased risk; thus, adalimumab was presumed to have higher risk than etanercept. Malisiewicz et al. described three cases of significant eosinophilia in relation to adalimumab use; the switch from adalimumab to etanercept was however tolerated [26].

Summary

- Anti-TNF-related eosinophilia have shown to typically resolve within a month of drug discontinuation but, in some instances, has been shown to linger for several months after.

- Switching between the same classes of drugs should probably be done with caution to prevent further episodes of eosinophilia.

Other reported side effects Bessisow et al. identified 69 cases of venous thrombosis and 20 cases of arterial thrombosis in patients treated with anti-TNF agents. Although these cases were reported to be associated with anti-TNF, the association was very nebulous due to the multitude of potential confounders including the underlying disease process which was felt to be the most likely culprit [3]. As such, discontinuation of therapy was not recommended in these situations. Henoch-Schönlein purpura is another effect that has been reported with anti-TNF therapy [27]. The switch between two different TNF inhibitors (adalimumab to infliximab) has been successful in some case reports [28]. Hemophilia A has been reported in a few case reports, mainly with adalimumab and etanercept [29–31]. In a case described by Banse et al., a possible association with etanercept and acquired hemophilia unresponsive to steroids and rituximab (ultimately responding to azathioprine) was discussed [30]. Acquired erythrocytosis has also been reported with infliximab therapy. The postulated mechanism is that anti-TNF agents suppress the action of TNF-alpha in the bone marrow (apoptosis), which in turn leads to erythrocytosis [32]. Lymphocytosis, factor XI deficiency (with adalimumab use), and pancytopenia [32–36] have been reported as well.

IL-6 inhibitors

These are widely used in patients with rheumatoid arthritis, Castleman disease, giant cell arthritis, and COVID-19 (tocilizumab) [1]. Tocilizumab and sarilumab are medications under this class. The current literature supports neutropenia and eosinophilia as side effects associated with the use of these agents.

Neutropenia IL-6 inhibitors are known to be associated with neutropenia, which is usually transient and dose-dependent [37]. The mechanism is thought to be due to inhibition of biologic effect of IL-6 on the recruitment of neutrophils in the peripheral blood [38–40].

A case series and review of the literature by Showman et al. analyzed the course of four patients who developed neutropenia after intravenous tocilizumab treatment at a dose of 8 mg/kg. The neutropenia improved after a dose reduction by 10–20% suggesting a dose-dependent relationship [39]. Moreover, they alluded to the fact that a history of neutropenia in response to other DMARDs might be a potential predictive factor for neutropenia induced by tocilizumab.

Espinoza et al. reported a retrospective cohort of patients with rheumatic diseases treated with three different classes of intravenous biological DMARDs (499 patients treated with either abatacept, infliximab, or tocilizumab); among which, tocilizumab resulted in neutropenia more frequently in comparison to abatacept or infliximab (18.6 vs 3.8% and 2.8%, respectively, $p < 0.001$). The mean reduction in ANC (absolute neutrophil count) with tocilizumab was 32% compared to the baseline. They demonstrated a dose–response relationship to neutropenia: 7.2% in those receiving 6 mg/kg of tocilizumab compared to 25.8% in those receiving 8 mg/kg. The onset of neutropenia occurred within the first 3 months, but was also reported after a year of use. Patients with a history of neutropenia with methotrexate or concomitant treatment with methotrexate were more prone to neutropenia [41].

In a randomized controlled trial by Fleishmann et al., comparing placebo with sarilumab (546 patients, of which 454 were treated with sarilumab), to evaluate long-term safety and efficacy over 5 years in patients with rheumatoid arthritis refractory to TNF alpha inhibitors, neutropenia was found to be the most common adverse effect: 15.3 per 100 PY. ANC of $< 1000 \text{ cells/mm}^3$ was observed in 74 patients receiving any dose of sarilumab that was 14% of the patients [38]. Likewise, a trial comparing adalimumab to sarilumab monotherapy (Burmester et al.) for rheumatoid arthritis showed that the rate of neutropenia was more with sarilumab therapy with three people in the sarilumab group experiencing severe neutropenia, $\text{ANC} < 0.5 \text{ G/L}$ (Neutropenia was observed in one patient in adalimumab group among 185 and 25 in the sarilumab group among 184) [40]. However, an increase in the incidence of infection was not observed with increased severity of neutropenia. This disconnect was thought to be due to effect on neutrophil migration rather than loss of neutrophil function or apoptotic effects [37–39].

Summary

- Neutropenia is commonly seen with IL-6 inhibitors; however, it has not been seen to be typically associated with an increase incidence of infections.
- The side effect of neutropenia has been shown to be dose dependent, thus advising caution with incremental dose of IL-6 inhibitor therapies. Use of lowest effective dose should be considered.
- Patients with prior history of DMARD-associated neutropenia are at heightened risk of developing IL-6-induced neutropenia and thus regular monitoring of blood counts might be necessary.

Eosinophilia Morrisroe and Wong reported a case of tocilizumab-induced eosinophilia with gastrointestinal involvement, with an increase in eosinophil count after subsequent dosing. After stopping tocilizumab infusions, the peripheral eosinophilia started to decrease immediately and completely normalized within 2 months [42].

Other reported side effects Case reports have described acquired factor XIII deficiency associated with tocilizumab used for the treatment of rheumatoid arthritis [43].

B-cell depletion and inhibition

Rituximab and belimumab are used to treat various rheumatic diseases. Rituximab is known to be associated with hypogammaglobulinemia [44, 45]. Here, we will describe late-onset neutropenia (LON) with rituximab.

LON is one of the significant side effects of rituximab therapy, which is defined as an absolute blood neutrophil count (ANC) of $< 1.5 \times 10^9/\text{L}$ occurring 4 weeks after the last rituximab infusion [46–48]. Reitblat et al. described two cases of late-onset neutropenia with rituximab with spontaneous improvement upon drug withdrawal. There was no appearance of LON with rechallenge in both cases when given 6 months to 1 year after the episode [48]. Bone marrow biopsies in patients with LON have shown a lymphocyte predominant cell line comprising an average of 41% of the cellular aspirate, which could suggest that there is a reduction in granulopoiesis with rituximab use. Direct toxic effect, immune-mediated, and bone marrow infiltration by T-large granular lymphocytes are other reported mechanisms reported [48]. Ajeganova et al. reported the correlation of the FCGR3A V allele with the occurrence of LON conferring to a fourfold increase in the calculated odds ratio [46]. However, serious infections have not been reported and the recovery was reported to be usually spontaneous. Granulocyte colony stimulating factor (G-CSF) was shown to shorten the time to ANC recovery but did not change overall outcomes [47–49]. LON was not considered to be a contraindication to repeat treatment with Rituximab [48, 50, 51]. Breuer et al. advised vigilance with rituximab administration and follow-up of complete and differential blood counts in about 5 months [50].

Kinase inhibitors

Tofacitinib, baricitinib, upadacitinib, peficitinib, and filgotinib are orally administered kinase inhibitors that are used primarily in rheumatoid arthritis with an inadequate response to DMARDs.

Neutropenia Schulze-Koops et al. analyzed changes in neutrophil counts, lymphocyte counts, and hemoglobin levels in patients on tofacitinib for rheumatoid arthritis from six phase-3 randomized controlled trials ($n = 4721$) and two long-term extension (LTE) studies ($n = 4858$). They concluded that treatment with tofacitinib can cause a decrease in neutrophils but they usually stabilize with long-term treatment. It was thought to be due to inhibition of JAK-dependent IL-6 signaling, which was consistent with IL-6-induced neutropenia. A gradual reduction of the mean lymphocyte count was also shown, which stabilized over time. There was an initial increase in hemoglobin level which later stabilized in the LTE studies. Clinically meaningful reduction in hemoglobin level was not observed ($< 1\%$) [52].

Thrombocytopenia Kadoba et al. described a case of severe thrombocytopenia in the context of possible TAFRO syndrome (thrombocytopenia, anasarca, fever, elevated CRP and creatinine levels, hepatosplenomegaly, and lymphadenopathy) in a patient with history of rheumatoid arthritis on tofacitinib therapy. It initially responded to discontinuation of the drug but upon recurrence, it was shown to be refractory to steroids and rituximab [53].

Summary

- The hematological side effects of kinase inhibitors should likely be studied further.
- Regular monitoring of complete and differential counts during therapy might be necessary.

Costimulation blockage

Abatacept is available for use in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. Espinoza et al. analyzed 499 patients treated with abatacept, infliximab, or tocilizumab, and the rate of neutropenia in patients taking abatacept was noted to be 3.8%. All patients receiving abatacept continued treatments without adjusting dosage or infusion interval [41].

IL-1 inhibitors

Anakinra, canakinumab, and rilonacept are used in the treatment of various rheumatological conditions, including familial mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), TNF-1 associated periodic syndrome (TRAPS), and rarely in rheumatoid arthritis due to their modest effect on inflammatory arthritis as compared to other biological agents [1]. The current literature describes

neutropenia and thrombocytopenia as hematological side effects associated with these agents.

Neutropenia There have been some case reports describing neutropenia with anakinra and canakinumab [54, 55].

Thrombocytopenia Den Broeder et al. identified thrombocytopenia as one of the serious adverse events in an observational study on the efficacy, safety, and drug survival of anakinra in patients with rheumatoid arthritis. Causality was established with rechallenge and thrombocytopenia improved after drug cessation [56]. However, Quartuccio and De Vita reported an association without confirmed causality (no recurrence at rechallenge) with IL-1 antagonists [57].

IL-12/23 inhibitors

Ustekinumab and guselkumab are used in psoriatic arthritis, psoriasis, and Crohn's disease. There have been reports of thrombocytopenia with ustekinumab [15]. Due to limited research, a causal-link has not been adequately established.

IL-17 inhibitors

Secukinumab and ixekizumab are two drugs in this class that are available for use in psoriasis, psoriatic arthritis, ankylosing spondylitis, and are also being investigated for uveitis [1]. The hematologic side effects described below have been reported in patients treated with these drugs.

Thrombocytopenia Nakahara et al. described thrombocytopenia in a patient sequentially treated with adalimumab, secukinumab, and ustekinumab. The most severe thrombocytopenia was observed during the switch from adalimumab to secukinumab. The mechanism was, however, unclear [15].

Henoch-Schönlein purpura Reverte et al. described a case of Henoch-Schönlein purpura (HSP) in a patient treated with secukinumab for psoriasis, successfully replaced by etanercept without recurrence of HSP [58].

Eosinophilia Hayashi et al. described a case of brodalumab-associated pleural effusion noted to have massive eosinophil infiltration on cytopathological evaluation. Brodalumab was then stopped and switched to secukinumab. In this report, secukinumab was stopped and switched to the infliximab due to recurrence of effusion. The mechanism was thought to be secondary to stimulation of Th2 genes to induce eosinophilia via Th2 cytokine production [59].

Conclusion

In recent decades, the routine use of biologic agents for treatment of various rheumatic diseases has dramatically risen. These newly developed agents have extended our treatment options and have demonstrated abundant success. Given the increased use, it has become pivotal for clinicians to readily identify their side effects. After thorough review of the literature, it becomes clear that there are a range of hematologic complications associated with biologic agents used for rheumatic diseases. Close monitoring of blood differentials becomes crucial in identifying side effects. Although the literature on this topic is scattered, there is clear benefit to organizing it for clinical reference. After careful analysis, there are several key points which can be distilled from this review:

- a. Switching between the same classes of biologics might not be the best option if the hematologic complication was severe in terms of infection/target organ damage. Switching to a different class of biologic would likely be the preferred course.
- b. The side effects (particularly with IL-6 inhibitors) are shown to be dose-dependent. These drugs should be titrated down to the minimum dose as possible to achieve therapeutic response. Especially for patients with prior history of similar adverse events. (For example, reducing dose of tocilizumab in patients with prior history of neutropenia with any DMARDs).
- c. A prior history of neutropenia associated with DMARD therapy is likely a strong indicator that a patient may develop neutropenia with the use of a biologic agent.
- d. Typically, hematologic side effects have shown to resolve with drug discontinuation. Longer and repeated exposure might lead to longer-lasting complications and decreased rates of normalization.
- e. Obtaining a baseline complete and differential blood count with regular monitoring during and after therapy is likely of very high importance.
- f. Among patients on biologics who present with anemia, TTP should likely be considered in the differentials.
- g. There is much work to be done in this evolving field. Only with further study can we better understand the mechanisms of the various complications.

Acknowledgements A special thank you to Ms. Amanda Pomeroy, a medical librarian at Danbury Hospital, for assistance with the literature review.

Declarations

Conflict The authors declare no competing interests. This article does not contain any studies with human participants performed by any of

the authors. Thus, informed consent was not required. No financial or non-financial disclosures to make.

References

1. Furst DE (2017) Overview of biologic agents and kinase inhibitors in the rheumatic diseases - UpToDate. UpToDate. Published online
2. Tanaka Y (2021) Recent progress in treatments of rheumatoid arthritis: an overview of developments in biologics and small molecules, and remaining unmet needs. *Rheumatology* 60(Supplement_6):vi12–vi20. <https://doi.org/10.1093/rheumatology/keab609>
3. Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Van Assche G (2012) Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther* 36(4):312–323. <https://doi.org/10.1111/j.1365-2036.2012.05189.x>
4. Feuerstein JD, Cheifetz AS (2014) Miscellaneous adverse events with biologic agents (excludes infection and malignancy). *Gastroenterol Clin N Am* 43(3):543–563. <https://doi.org/10.1016/j.gtc.2014.05.002>
5. Sebastian S, Ashton K, Houston Y, Diggory TM, Dore P (2012) Anti-TNF therapy induced immune neutropenia in Crohns disease- report of 2 cases and review of literature. *J Crohns Colitis* 6(6):713–716. <https://doi.org/10.1016/j.crohns.2012.01.014>
6. Favalli EG, Varena M, Sinigaglia L (2005) Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthritis. *Clin Exp Rheumatol* 23(2):247–250
7. Shivaji UN, Sharratt CL, Thomas T et al (2019) Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 49(6):664–680. <https://doi.org/10.1111/apt.15097>
8. Datta K, Ghosh RK, Ghosh SM (2010) Serious neutropenia following etanercept administration in a 62 years female patient of rheumatoid arthritis. *J Assoc Physicians India* 58:643–644
9. Theodoridou A, Kartsios C, Yiannaki E, Markala D, Settas L (2006) Reversible T-large granular lymphocyte expansion and neutropenia associated with adalimumab therapy. *Rheumatol Int* 27(2):201–202. <https://doi.org/10.1007/s00296-006-0187-3>
10. Haroon M, Daly M, Harney S (2012) Re-challenge with etanercept in patients with etanercept-induced neutropenia. *Clin Rheumatol* 31(1):151–155. <https://doi.org/10.1007/s10067-011-1822-2>
11. Falsetti L, Sampaolesi M, Riccomi F, Nitti C (2020) Adalimumab as a potential cause of drug-induced thrombocytopenic microangiopathy. *BMJ Case Rep* 13(3). <https://doi.org/10.1136/bcr-2019-233526>
12. Cepeda J, Liedke C, Patnaik A, Yao Q (2018) Development of thrombotic thrombocytopenic purpura in association with the monoclonal antibody, golimumab, used to treat rheumatoid arthritis, in a case with literature review. *J Clin Rheumatol* 24(4):229–231. <https://doi.org/10.1097/RHU.0000000000000684>
13. Baysal M, Ümit EG, Santaş F, Kodal NS, Demir AM (2018) Drug induced thrombotic microangiopathy with certolizumab pegol. *Balk Med J* 35(5):398–399. <https://doi.org/10.4274/balkanmedj.2017.1224>
14. Harada Y, Yamamoto H, Sato M, Kodaira M, Kono T (2015) Autoimmune hemolytic anemia during adalimumab treatment for plaque psoriasis. *Intern Med* 54(9):1103–1104. <https://doi.org/10.2169/internalmedicine.54.3433>
15. Nakahara T, Konishi S, Yasukochi Y et al (2019) Thrombocytopenia in a psoriatic patient sequentially treated with adalimumab, secukinumab and ustekinumab. *J Dermatol* 46(5):e157–e158. <https://doi.org/10.1111/1346-8138.14681>

16. Casanova MJ, Chaparro M, Martínez S, Vicuña I, Gisbert JP (2012) Severe adalimumab-induced thrombocytopenia in a patient with Crohn's disease. *J Crohns Colitis* 6(10):1034–1037. <https://doi.org/10.1016/j.crohns.2012.04.001>
17. Boiten HJ, Amini S, Wolfhagen FHJ, Westerweel PE (2021) Adalimumab-induced platelet antibodies resulting in severe thrombocytopenia. *Br J Clin Pharmacol* 87(9):3619–3621. <https://doi.org/10.1111/bcp.14778>
18. Hamaguchi M, Kawahito Y, Ishino H, Yoshida M, Yoshikawa T (2007) A case report of tumor necrosis factor-alpha antibody-induced thrombocytopenia associated with emerging IgM anticardiolipin antibody in patients with scleroderma overlap/rheumatoid arthritis. *Clin Rheumatol* 26(6):988–990. <https://doi.org/10.1007/s10067-006-0229-y>
19. Brunasso AMG, Massone C (2009) Thrombocytopenia associated with the use of anti-tumor necrosis factor-alpha agents for psoriasis. *J Am Acad Dermatol* 60(5):781–785. <https://doi.org/10.1016/j.jaad.2008.12.001>
20. Pathare SK, Heycock C, Hamilton J (2006) TNFalpha blocker-induced thrombocytopenia. *Rheumatology* 45(10):1313–1314. <https://doi.org/10.1093/rheumatology/kei204>
21. Chiriac A, Brzezinski P, Stolnicu S et al (2016) Eosinophilia—a rare possible adverse reaction during anti-tumor necrosis factor-alpha therapy for psoriasis. *J Dermatol Treat* 27(2):110–113. <https://doi.org/10.3109/09546634.2015.1079299>
22. Vester K, Rüger RD, Harth W, Simon JC (2012) Transient blood eosinophilia during treatment with Adalimumab. *J Eur Acad Dermatol Venereol* 26(7):924–925. <https://doi.org/10.1111/j.1468-3083.2011.04169.x>
23. Nadeem I, Khatana U, Rasool MU, Wasil A, Azher M (2020) Lessons of the month 2: Chronic eosinophilic pneumonia (CEP): a rare manifestation of infliximab therapy. *Clin Med* 20(4):435–437. <https://doi.org/10.7861/clinmed.2020-0271>
24. Dabas G, De D, Handa S, Chatterjee D, Radotra BD (2018) Wells syndrome in a patient receiving adalimumab biosimilar: a case report and review of literature. *Indian J Dermatol Venereol Leprol* 84(5):594–599. https://doi.org/10.4103/ijdv.IJDVL_636_17
25. Adamson R, Yazici Y, Katz ES, Greisman SG, Steiger D (2013) Fatal acute necrotizing eosinophilic myocarditis temporally related to use of adalimumab in a patient with relapsing poly-chondritis. *J Clin Rheumatol* 19(7):386–389. <https://doi.org/10.1097/RHU.0b013e3182a701cb>
26. Malisiewicz B, Murer C, Pachlopnik Schmid J, French LE, Schmid-Grendelmeier P, Navarini AA (2011) Eosinophilia during psoriasis treatment with TNF antagonists. *Dermatology* 223(4):311–315. <https://doi.org/10.1159/000334805>
27. Pinheiro RR, Lencastre A (2017) Henoch-Schönlein purpura during anti-TNFα therapy: a fortuitous event or an indication to stop therapy? *Eur J Dermatol* 27(3):304–305. <https://doi.org/10.1684/ejd.2017.2979>
28. Marques I, Lagos A, Reis J, Pinto A, Neves B (2012) Reversible Henoch-Schönlein purpura complicating adalimumab therapy. *J Crohns Colitis* 6(7):796–799. <https://doi.org/10.1016/j.crohns.2012.02.019>
29. Yamaguchi T, Itoh M, Umezawa Y, Asahina A, Hanabusa H, Nakagawa H (2017) Acquired hemophilia A and fulminant diabetes mellitus possibly caused by adalimumab in a patient with psoriatic arthritis. *J Dermatol* 44(3):e3–e4. <https://doi.org/10.1111/1346-8138.13468>
30. Banse C, Benhamou Y, Lequerré T, Le Cam-Duchez V, Lévesque H, Vittecoq O (2015) Acquired hemophilia possibly induced by etanercept in a patient with rheumatoid arthritis. *Joint Bone Spine* 82(3):200–202. <https://doi.org/10.1016/j.jbspin.2014.12.003>
31. Arthanari S, Ahmad H, Nisar M (2012) Fatal acquired hemophilia A in a patient with rheumatoid arthritis treated with adalimumab. *J Clin Rheumatol* 18(1):50–51. <https://doi.org/10.1097/RHU.0b013e31823ee3cd>
32. Antonelli M, Bupathi M, Janakiram M, Hergenroeder P, Khan MA (2011) Acquired erythrocytosis upon treatment with infliximab for ankylosing spondylitis. *J Rheumatol* 38(3):581–583. <https://doi.org/10.3899/jrheum.101013>
33. Covach A, Leith CP, Rajguru SA, Yang DT (2015) A unique CD4+ large granular lymphocytosis occurring in patients treated with tumor necrosis factor α inhibitors: report of 2 cases. *Hum Pathol* 46(8):1237–1241. <https://doi.org/10.1016/j.humpath.2015.04.015>
34. Cetin G, Karatoprak C, Kiskac M, Zorlu M, Rezvani A, Cikriocioglu MA (2014) Factor XI deficiency diagnosed following use of adalimumab. *Indian J Pharmacol* 46(5):553–554. <https://doi.org/10.4103/0253-7613.140596>
35. Martínez Santana V, Izquierdo Navarro M, Calleja Hernández MÁ, Sánchez Sánchez T, Sainz GM (2012) Severe pancytopenia following etanercept administration in rheumatoid arthritis. *Int J Rheum Dis* 15(4):e78–79. <https://doi.org/10.1111/j.1756-185X.2012.01740.x>
36. Menon Y, Cucurull E, Espinoza LR (2003) Pancytopenia in a patient with scleroderma treated with infliximab. *Rheumatology* 42(10):1273–1274; author reply 1274. <https://doi.org/10.1093/rheumatology/keg341>
37. Nakamura I, Omata Y, Naito M, Ito K (2009) Blockade of interleukin 6 signaling induces marked neutropenia in patients with rheumatoid arthritis. *J Rheumatol* 36(2):459–460. <https://doi.org/10.3899/jrheum.080930>
38. Fleischmann R, Genovese MC, Maslova K, Leher H, Praestgaard A, Burmester GR (2021) Long-term safety and efficacy of sarilumab over 5 years in patients with rheumatoid arthritis refractory to TNF inhibitors. *Rheumatology* 60(11):4991–5001. <https://doi.org/10.1093/rheumatology/keab355>
39. Shovman O, Shoenfeld Y, Langevitz P (2015) Tocilizumab-induced neutropenia in rheumatoid arthritis patients with previous history of neutropenia: case series and review of literature. *Immunol Res* 61(1–2):164–168. <https://doi.org/10.1007/s12026-014-8590-4>
40. Burmester GR, Lin Y, Patel R et al (2017) Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MON-ARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis* 76(5):840–847. <https://doi.org/10.1136/annrheumdis-2016-210310>
41. Espinoza F, Le Blay P, Combe B (2017) Biologic disease-modifying antirheumatic drug (bDMARD)-induced neutropenia: a registry from a retrospective cohort of patients with rheumatic diseases treated with 3 classes of intravenous bDMARD. *J Rheumatol* 44(6):844–849. <https://doi.org/10.3899/jrheum.150457>
42. Morrisroe K, Wong M (2015) Drug-induced hypereosinophilia related to tocilizumab therapy for rheumatoid arthritis. *Rheumatology* 54(11):2113–2114. <https://doi.org/10.1093/rheumatology/kev275>
43. Matsuoka M, Majima T, Onodera T et al (2012) Hemorrhagic-acquired factor XIII deficiency associated with tocilizumab for treatment of rheumatoid arthritis. *Int J Hematol* 96(6):781–785. <https://doi.org/10.1007/s12185-012-1191-x>
44. Boleto G, Avouac J, Wipff J et al (2018) Predictors of hypogammaglobulinemia during rituximab maintenance therapy in rheumatoid arthritis: a 12-year longitudinal multi-center study. *Semin Arthritis Rheum* 48(2):149–154. <https://doi.org/10.1016/j.semarthrit.2018.02.010>
45. Evangelatos G, Fragoulis GE, Klavdianou K, Moschopoulou M, Vassilopoulos D, Iliopoulos A (2021) Hypogammaglobulinemia after rituximab for rheumatoid arthritis is not rare and is related

- with good response: 13 years real-life experience. *Rheumatology* 60(5):2375–2382. <https://doi.org/10.1093/rheumatology/keaa617>
46. Ajeganova S, Tesfa D, Häggglund H et al (2017) Effect of FCGR polymorphism on the occurrence of late-onset neutropenia and flare-free survival in rheumatic patients treated with rituximab. *Arthritis Res Ther* 19(1):44. <https://doi.org/10.1186/s13075-017-1241-0>
 47. Monaco WE, Jones JD, Rigby WFC (2016) Rituximab associated late-onset neutropenia—a rheumatology case series and review of the literature. *Clin Rheumatol* 35(10):2457–2462. <https://doi.org/10.1007/s10067-016-3313-y>
 48. Reitblat T, Wechsler A, Reitblat O (2015) Rituximab-related late-onset neutropenia in patients with rheumatic diseases: successful re-challenge of the treatment. *Am J Case Rep* 16:211–214. <https://doi.org/10.12659/AJCR.892541>
 49. Abdulkader R, Dharmapalaiah C, Rose G, Shand LM, Clunie GP, Watts RA (2014) Late-onset neutropenia in patients with rheumatoid arthritis after treatment with rituximab. *J Rheumatol* 41(5):858–861. <https://doi.org/10.3899/jrheum.130526>
 50. Breuer GS, Ehrenfeld M, Rosner I et al (2014) Late-onset neutropenia following rituximab treatment for rheumatologic conditions. *Clin Rheumatol* 33(9):1337–1340. <https://doi.org/10.1007/s10067-014-2562-x>
 51. Besada E, Koldingsnes W, Nossent J (2012) Characteristics of late onset neutropenia in rheumatologic patients treated with rituximab: a case review analysis from a single center. *QJM* 105(6):545–550. <https://doi.org/10.1093/qjmed/hcs015>
 52. Schulze-Koops H, Strand V, Nduaka C et al (2017) Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across phase 3 and long-term extension studies. *Rheumatology* 56(1):46–57. <https://doi.org/10.1093/rheumatology/kew329>
 53. Kadoba K, Waki D, Nishimura K et al (2020) Development of severe thrombocytopenia with TAFRO syndrome-like features in a patient with rheumatoid arthritis treated with a Janus kinase inhibitor: a case report. *Medicine (Baltimore)* 99(42):e22793. <https://doi.org/10.1097/MD.00000000000022793>
 54. Perrin F, Néel A, Graveleau J, Ruellan AL, Masseau A, Hamidou M (2014) Two cases of anakinra-induced neutropenia during auto-inflammatory diseases: drug reintroduction can be successful. *Presse Med* 43(3):319–321. <https://doi.org/10.1016/j.lpm.2013.06.028>
 55. Lyseng-Williamson KA (2013) Canakinumab: a guide to its use in acute gouty arthritis flares. *BioDrugs* 27(4):401–406. <https://doi.org/10.1007/s40259-013-0037-2>
 56. den Broeder AA, de Jong E, Franssen MJAM, Jeurissen MEC, Flendrie M, van den Hoogen FHJ (2006) Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 65(6):760–762. <https://doi.org/10.1136/ard.2004.033662>
 57. Quartuccio L, De Vita S (2007) Interleukin 1 receptor antagonist therapy-induced thrombocytopenia in adult onset Still's disease. *J Rheumatol* 34(4):892–893
 58. Reverte M, Etienne M, Fouchard M, Doucet L, Brenaut E, Misery L (2019) Occurrence of Henoch-Schönlein purpura in a patient treated with secukinumab. *J Eur Acad Dermatol Venereol* 33(12):e455–e457. <https://doi.org/10.1111/jdv.15776>
 59. Hayashi W, Osada SI, Toyoshima A et al (2019) Pleural fluid eosinophilia: a possible adverse event of interleukin-17 inhibition. *Acta Derm Venereol* 99(12):1174–1175. <https://doi.org/10.2340/00015555-3311>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.