

Successful Switch to Golimumab for Eosinophilia and Skin Symptoms Related to Multiple Biologics in a Patient with Rheumatoid Arthritis

Naoto Azuma¹, Kiyoshi Matsui¹, Naoaki Hashimoto^{1,2},
Takahiro Yoshikawa¹ and Hajime Sano¹

Abstract

Biologics used in the treatment of rheumatoid arthritis (RA) rarely cause eosinophilia. We herein report a patient with RA being treated with infliximab, adalimumab, and tocilizumab who developed eosinophilia with skin symptoms. Interestingly, the marked eosinophilia and skin symptoms did not reappear after the patient's medication was switched to golimumab. In this case, the presence of biologics-specific antibodies suggested that immunogenicity caused the eosinophilia. Therefore, switching to a biologic with a lower immunogenicity was effective. These findings may be helpful for clinicians treating patients with biologics-induced eosinophilia.

Key words: anti-drug antibody, biologics, eosinophilia, golimumab, hypersensitivity reaction, immunogenicity

(Intern Med 56: 1585-1590, 2017)

(DOI: 10.2169/internalmedicine.56.8168)

Introduction

Eosinophilia is a rare complication of rheumatoid arthritis (RA). Although the development of eosinophilia has been thought to reflect the severity or activity of RA (1, 2), this association has not been clearly established (3, 4). Eosinophilia in RA is more commonly caused by the medications used to manage it (4). In our review of the literature, eosinophilia and eosinophilia-associated diseases related to the use of the seven biologics approved for RA in Japan (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, tocilizumab, and abatacept) have not been reported frequently. As such, due to the rarity of this condition, the mechanism of eosinophilia caused by these biologics remains unclear.

We herein report a patient with RA who developed eosinophilia with skin symptoms while being treated with the biologics infliximab, adalimumab, and tocilizumab. Interestingly, marked eosinophilia and skin symptoms were not observed in this patient for one year after switching to

golimumab. In this case, the presence of biologics-specific antibodies suggested that immunogenicity caused the eosinophilia. No previous reports have shown the presence of biologics-specific antibodies in RA patients with biologics-induced eosinophilia. In addition, this is the first report of a successful switch to golimumab for preventing eosinophilia caused by the biologics for RA. This may be helpful in the treatment of RA patients with refractory eosinophilia and eosinophilia-associated diseases caused by biologics.

Case Report

A 43-year-old Japanese woman diagnosed with RA in 2000 (at 27 years of age) was initially treated with low-dose oral prednisolone (PSL; 7.5 mg/day or less), methotrexate (MTX; 7.5 mg/week), and sodium aurothiomalate. She had no previous history of allergic diseases, including drug allergies. In June 2004, she was switched to infliximab (3 mg/kg every 8 weeks, intravenous drip infusion) due to the persistence of active polyarthritis (Disease Activity Score in 28 joints using C-reactive protein [DAS28-CRP]: 4.28) and the

¹Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Japan and ²Hashimoto Clinic for Rheumatic Diseases, Japan

Received for publication August 23, 2016; Accepted for publication October 17, 2016

Correspondence to Dr. Naoto Azuma, naoazuuh@hyo-med.ac.jp

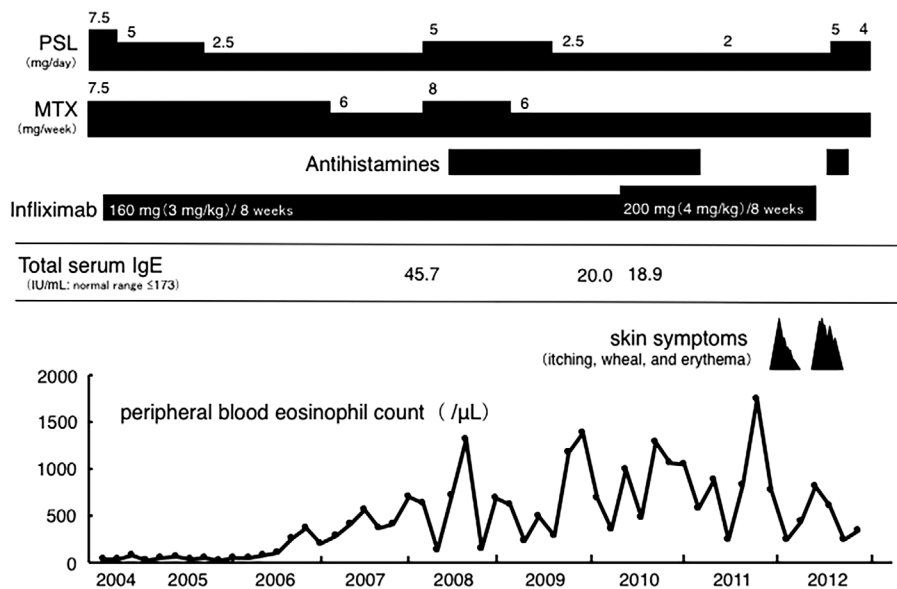


Figure 1. Clinical course during treatment with infliximab. PSL: prednisolone, MTX: methotrexate, IgE: immunoglobulin E

progression of bone joint destruction as indicated by X-rays. Infliximab therapy produced an adequate and prompt clinical response. Combination therapy with infliximab, low-dose PSL (2.5-5 mg/day), and MTX (6 mg/week) maintained the remission of her RA disease activity. The dose of infliximab was increased (4 mg/kg every 8 weeks) to control the slight exacerbation of her arthritis (DAS28-CRP: 2.35-3.34) that occurred during the tapering of the PSL dose. It was difficult to increase the dose of MTX to more than 6 mg/week because of nausea.

From July 2006 (15th injection), her peripheral blood eosinophil count gradually started to increase; however, the total serum immunoglobulin E (IgE) levels (45.7 IU/mL; normal range \leq 173) and other blood cell counts were normal, and no skin symptoms were observed. The eosinophilia worsened (maximum: 1,745/ μ L) despite the administration of antihistamines and an increase in the PSL dose. There had been no changes in her usual medication. No other causes of eosinophilia, such as malignancy, infection, allergic diseases, or other autoimmune diseases, could be identified. Although we speculated that the eosinophilia was due to an adverse reaction to infliximab, the treatment was continued because the patient's RA disease activity was well controlled (DAS28-CRP: $<$ 2).

However, in December 2011 (49th injection), she experienced intense and widespread itching with wheal formation and erythema 30 minutes after starting of infliximab injection. Subsequently, these skin symptoms occurred within 30 minutes after starting the administration of infliximab each time she received the injection and disappeared immediately with intravenous hydrocortisone. This occurred despite prophylactic treatment (intravenous hydrocortisone injection and oral antihistamine). After the discontinuation of infliximab (last injection: May 2012, 52nd injection), her skin symptoms disappeared, and her eosinophil count returned to a

normal value within approximately three months (Fig. 1).

Adalimumab was initiated (40 mg every two weeks, subcutaneous injection) in December 2012 because her polyarthritis had deteriorated (DAS28-CRP: 4.02). This resulted in a rapid clinical improvement, and the patient's RA remained in remission. However, in February 2013 (4th injection), the eosinophilia reappeared and worsened progressively. From then on, she also developed persistent intense itching over her entire body throughout the interval between injections, without any injection-site reactions or eruptions such as wheals or erythema. Dermographism was positive. The total serum IgE levels remained within the normal range (32.0 IU/mL). Antihistamines were ineffective, so adalimumab was stopped (final injection: April 2013, 7th injection). This resulted in the remission of the itching; however, her eosinophil count rose to 4,878/ μ L. Aside from the skin symptoms, no other organ manifestations attributable to hypereosinophilia were observed. Increasing her oral PSL dose (10 mg/day) resolved the itching and eosinophilia (Fig. 2).

Because the patient's RA disease activity was only partially controlled (DAS28-CRP: 3.85), tocilizumab was started (162 mg every 2 weeks, subcutaneous injection) in July 2013. The polyarthritis promptly disappeared, and her RA remained in remission. However, from August 2013 (3rd injection) onward, despite the concomitant administration of antihistamines, the widespread itching reappeared and continued throughout the interval between injections, without the development of injection-site reactions or eruptions.

From July 2014 (20th injection), she developed severe injection-site reactions, such as itching, erythema, and swelling, along with erythema with itching over her entire body, both of which occurred several hours after each tocilizumab injection and lasted for a few days. The eosinophilia also reappeared (maximum: 1,895/ μ L). In addition, the total serum IgE levels (306 IU/mL), serum tocilizumab-specific IgE an-

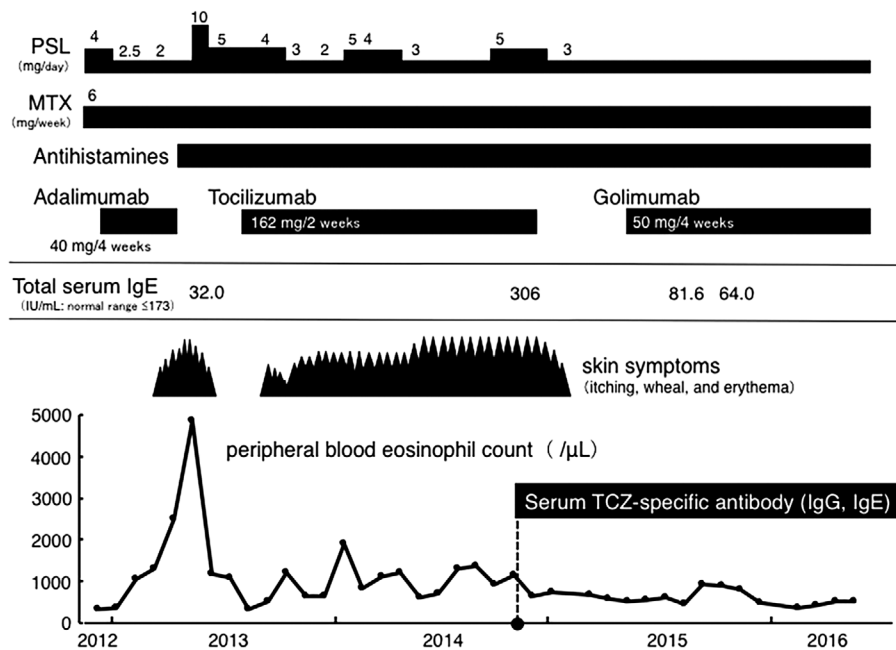


Figure 2. Clinical course during treatment with adalimumab, tocilizumab, and golimumab. PSL: prednisolone, MTX: methotrexate, IgG: immunoglobulin G, IgE: immunoglobulin E

tibody levels as measured by fluorescence enzyme immunoassay (FEIA) (6.64 UA/mL; reference standard range ≤ 0.34), and serum tocilizumab-specific IgG antibody levels as measured by enzyme-linked immunosorbent assay (ELISA) (43.0 ng/mL; reference standard range ≤ 3.91) were found to be elevated in November 2014. Based on these findings, tocilizumab was discontinued, despite the patient's RA disease activity being well controlled (DAS28-CRP: <1.5) (final injection: January 2015, 35th injection). Consequently, the skin symptoms disappeared, and the eosinophil count and total serum IgE levels returned to their normal ranges within a few months (Fig. 2).

At this point, the patient was only being treated with low-dose oral PSL (3 mg/day) and methotrexate (6 mg/week). As a result, her polyarthritis flared again (DAS28-CRP: 3.21). Golimumab was started in May 2015, and her RA disease activity rapidly went into remission. Remarkably, the marked eosinophilia and skin symptoms, such as injection-site reactions, eruption, or itching on her body other than at the injection site, did not reappear, even after one year on golimumab, although golimumab was co-administered with antihistamines. Her eosinophil count has remained at $\leq 1,000/\mu\text{L}$ or less (mostly around $500/\mu\text{L}$) while on golimumab (Fig. 2), and her RA disease activity is well-controlled (DAS28-CRP: <2.0).

Discussion

This report describes a case of persistent eosinophilia with skin symptoms attributable to three biologics (infliximab, adalimumab, and tocilizumab) for the treatment of RA, and the successful switch to golimumab to avoid these adverse reactions. Eosinophilia is rare in RA, occurring only

in approximately 7% of RA patients (4, 5). Although some investigators have reported that the development of eosinophilia reflects the severity or activity of RA (1, 2), the mechanisms of this association are still not clearly understood. Instead, it is speculated that eosinophilia may be caused by the medications used to treat RA (4).

In the eHealthMe database, eosinophilia was found in 0.035% of patients who experienced side effects while undergoing treatment with any of the 7 biologic agents approved for RA in Japan (infliximab 0.07%, etanercept 0.03%, adalimumab 0.05%, golimumab 0.03%, certolizumab pegol 0%, tocilizumab 0.35%, and abatacept 0.13%) (6). In our review of the literature, eosinophilia and eosinophilia-associated diseases related to these biologics have only been reported sporadically (Table) (7-19). Cases of eosinophilia-onset or associated symptoms have been most frequently reported in patients treated with adalimumab, followed by etanercept, and then infliximab. Adalimumab-related reports mostly comprised cases with diseases other than RA. According to the eHealthMe database, tocilizumab was the most frequent cause of eosinophilia among those seven biologics; however, there was only one tocilizumab-related report in the literature (18). The time to symptom onset after the administration of each biologic varied. There were no reports of eosinophilic disorders in patients treated with golimumab, certolizumab pegol, or abatacept. As such, eosinophilia or eosinophilia-associated diseases related to these biologics may be considered a rare adverse reaction.

In our case, the patient's RA disease activity remained in remission under treatment with every biologic used until she developed eosinophilia with skin symptoms. Other causes of eosinophilia were excluded. A skin biopsy was not performed because the patient did not provide informed consent

Table. Previous Reports of Eosinophilia and Eosinophilia-associated Diseases Related to Biologics Approved for Rheumatoid Arthritis in Japan.

Reference	Age(years) /Sex	Underlying disease	Biologics	Period to onset*	Condition or symptom
7	57/F	RA	ETN	<24 hours after the 1st injection	Eosinophilic cellulitis
8	72/F	RA	ADA	3-4 hours after the 2nd injection	Eosinophilic cellulitis
9	80/F	RA	1) IFX 2) ETN	3 months 1 month	Eosinophilia, subacute prurigo Eosinophilia, subacute prurigo
10	46/M 55/F 24/M	PsA PsA Psoriasis	ADA ADA 1) ETN 2) ADA	3.25 months 11 months N.S.† N.S.†	Eosinophilia (No relapse after switch to ETN) Eosinophilia Eosinophilia Eosinophilia
11	16/M	CD	1) IFX 2) ADA	2 weeks 1 week	Eosinophilia, pruritus, erythema Eosinophilia
12	69/F	RA	IFX	1 week (9 years‡)	Eosinophilic cellulitis Eosinophilia
13	58/F	Hallopeau	ADA	1 month	Eosinophilia (transient) (No relapse after rechallenge)
14	51/F	RP	ADA	15 days after the 1st injection	Acute necrotizing eosinophilic myocarditis
15	59/M	PsA	1) ETN 2) ADA	1 month 5 months	Eosinophilia Eosinophilia
16	24/F	RA	ETN	3 years	Eosinophilia, digital vasculitis
17	51/M	CD	ADA	1 year	Eosinophilic granulomatosis with polyangiitis (EGPA)
18	52/F	RA	TCZ	1 month	Eosinophilia, Eosinophilic esophagitis and gastritis
19	66/M 34/F 55/F 57/M 38/M	PsA Psoriasis Psoriasis PsA Psoriasis	ADA ADA ADA ADA ADA	3 months 3 months 3 months 6 months 12 months	Eosinophilia Eosinophilia Eosinophilia Eosinophilia Eosinophilia

* Period to onset: Period to onset from administration of biologics

† N.S.: data not shown

‡ 9 years; Although skin involvement appeared 1 week after the administration of infliximab, the patient had received infliximab for 9 years. At that time, skin rash was diagnosed as eosinophilic cellulitis.

RA: rheumatoid arthritis, PsA: psoriatic arthritis, CD: Crohn's disease, Hallopeau: acrodermatitis continua of Hallopeau, RP: relapsing polychondritis, IFX: infliximab, ETN: etanercept, ADA: adalimumab, TCZ: tocilizumab

for the procedure. Both the eosinophilia and the skin symptoms were ameliorated by discontinuation of the biologics used at the time. Based on these observations, it was speculated that her eosinophilia and skin symptoms were induced by infliximab, adalimumab, and tocilizumab. The mechanism of eosinophilia induction during biologic treatment is still unknown. The pharmaceutical additives in each biologic preparation were different, and there were no additives included in infliximab, adalimumab, and tocilizumab that were not also included in golimumab. Although various types of hypersensitivity reactions due to polysorbate 80 have previously been reported (20-23), this additive was used in all of these biologics. However, golimumab contained the least amount of polysorbate 80 among the 4 biologics: infliximab, 0.5 mg/vial (infliximab 100 mg); adalimumab, 0.8 mg/syringe (adalimumab 40 mg/0.8 mL); tocilizumab, 0.18 mg/auto-injector (tocilizumab 162 mg); golimumab 0.075 mg/

syringe (golimumab 50 mg). This difference in the polysorbate 80 content may have affected the development of eosinophilia with skin symptoms in this case.

Previous reports have hypothesized that the generation of IgE class-switched antibodies might lead to IgE-mediated drug hypersensitivity and subsequent eosinophilia (10, 15, 19). Biologics-specific IgE antibodies have been shown to mediate type I hypersensitivity reactions (24). In this case, although the skin symptoms that started during infliximab infusion appeared to be due to an immediate hypersensitivity reaction, infliximab-specific IgE antibodies were not measured, and the eosinophilia had been present for more than five years at that point in time. Although tocilizumab-specific IgE antibodies were positive, the skin symptoms appeared several hours after tocilizumab injection; thus, the tocilizumab induced a non-immediate hypersensitivity reaction. In addition, adalimumab administration

also produced a non-immediate reaction. Therefore, the patient's clinical symptoms could not be explained solely by IgE-mediated drug hypersensitivity. Recent reviews have shown that a non-immediate hypersensitivity reaction to biologics is caused by the production of biologics-specific IgG antibodies or the recruitment and activation of T cells against biologics. IgG forms immune complexes with biologics, and these complexes activate the complement cascade (25, 26). In this case, the only biologics-specific IgG antibodies that developed were the tocilizumab-specific IgG antibodies (IgG and IgE antibodies against infliximab and adalimumab were not examined). Although the mechanism of eosinophilia induction may differ across these three biologics, we speculate that the IgG/biologics immune complex-mediated complement activation and biologics-specific T cells-mediated reactions inducing a shift towards a T helper type 2 (Th2) immune response contributed to the patient's clinical symptoms. No previous reports have shown the presence of biologics-specific antibodies in RA patients with biologics-induced eosinophilia (7-19).

Biologics are large and complex molecules that are potentially immunogenic. Immunogenicity refers to the ability of a molecule to induce a specific humoral or cellular immune response. This unfavorable immune response leads to the development of anti-drug antibodies (ADAs), which not only affect the efficacy of biologics but also increases the risk of adverse events (27). Various types of ADAs have been observed during biologics treatment: mostly IgG, but also IgA, IgM, and rarely IgE (25, 27). The immunogenicity of the biologics can be verified by the development of ADAs. Immunogenicity varies among different biologics. Keiserman et al. (28) and Thomas et al. (29) reported that the frequencies of ADAs development against etanercept and golimumab were lower than those against other tumor necrosis factor (TNF) inhibitors (etanercept, 0-6%; golimumab, 0-7% vs. infliximab, 10-50%; adalimumab, 1-87%; and certolizumab pegol, 5-8%). With regard to non-TNF inhibitors, ADAs were detected in 3.5% of the subcutaneous tocilizumab injection monotherapy group and not detected at all in the intravenous tocilizumab infusion monotherapy group in a study of Japanese RA patients (30), in 2.8% of RA patients receiving intravenous abatacept therapy (with and without MTX) (31), and in approximately 4% of RA patients receiving subcutaneous abatacept therapy (with and without MTX) (32). Additionally, in a clinical trial in Japanese patients, serum tocilizumab-specific IgE antibodies were detected in 2.5% of patients treated with intravenous tocilizumab monotherapy for RA (33). These findings suggest that etanercept, golimumab, tocilizumab, and abatacept have lower immunogenicity than infliximab, adalimumab, and certolizumab pegol.

Beyond the above rationale, we decided to administer golimumab for the following reasons as well: [1] the patient had had a good clinical response to two TNF inhibitors (infliximab and adalimumab); [2] the patient preferred a biologic therapy with a relatively long interval between injections;

and [3] ADAs against golimumab have rarely developed in golimumab-treated patients who received concomitant MTX. In fact, the GO-FORTH trial conducted over 156 weeks in Japanese RA patients found that no patients developed ADAs in the 50 mg golimumab subcutaneous injection plus MTX therapy group, and only 1 (1.1%) patient tested positive for ADAs in the 100 mg golimumab subcutaneous injection plus MTX therapy group (MTX at a dose of 6-8 mg/week in both groups) (34, 35).

Golimumab is a fully human antibody produced in a human immunoglobulin transgenic mouse. This difference in the manufacturing process from other biologics was intended to contribute to a lower immunogenicity for golimumab (36). No marked eosinophilia or skin symptoms were observed in the patient in the year after switching to golimumab. Eosinophilia was previously considered a complication common to all TNF inhibitors, particularly in previous reports describing cases with eosinophilia induced by several TNF inhibitors (9, 10, 11, 15). However, one case report showed that eosinophilia had developed during adalimumab therapy did not reappear after switching to etanercept (10). The clinical courses in this case and in that previous report suggest that not all TNF inhibitors may be associated with eosinophilia as an adverse reaction.

To our knowledge, this is the first report of a successful switch to golimumab for preventing eosinophilia caused by other biologics used to treat RA. Thomas et al. showed in a systematic literature review that ADAs developed as early as 2 weeks but also as late as 3 years after the initiation of biologics treatment (29). In the GO-FORTH trial, ADAs against golimumab were detected more than one year after the initiation of therapy (34, 35). Because ADAs-mediated eosinophilia may occur later than this, a careful follow-up evaluation is necessary.

In the future, owing to an increase in the therapeutic use of biologics, the frequency of eosinophilia is likely to increase. Eosinophilia is a rare adverse reaction to the biologics used for RA treatment. Further studies are required to elucidate the association between eosinophilia and biologics. This case suggests that eosinophilia may be caused by immunogenicity of biologics, the severity of which varies among biologics. Clinicians should consider switching to biologics with lower immunogenicity (such as golimumab, in this case) when patients develop eosinophilia related to biologics. This could be helpful for RA patients with refractory eosinophilia related to biologics.

The authors state that they have no Conflict of Interest (COI).

References

1. Winchester RJ, Koffler D, Litwin SD, Kunkel HG. Observations on the eosinophilia of certain patients with rheumatoid arthritis. *Arthritis Rheum* **14**: 650-665, 1971.
2. Panush RS, Franco AE, Schur PH. Rheumatoid arthritis associated with eosinophilia. *Ann Intern Med* **75**: 199-205, 1971.

3. Rosenstein RK, Panush RS, Kramer N, Rosenstein ED. Hypereosinophilia and seroconversion of rheumatoid arthritis. *Clin Rheumatol* **33**: 1685-1688, 2014.
4. Kargili A, Baybek N, Kaya A, Koşar A, Karaaslan Y. Eosinophilia in rheumatologic diseases: a prospective study of 1000 cases. *Rheumatol Int* **24**: 321-324, 2004.
5. Chiardola F, Schneeberger EE, Citera G, et al. Prevalence and clinical significance of eosinophilia in patients with rheumatoid arthritis in Argentina. *J Clin Rheumatol* **14**: 211-213, 2008.
6. eHealthMe. [Internet]. [cited 2016 Aug 15]. Available from: <http://www.ehealthme.com>
7. Winfield H, Lain E, Horn T, Hoskyn J. Eosinophilic cellulitislike reaction to subcutaneous etanercept injection. *Arch Dermatol* **142**: 218-220, 2006.
8. Boura P, Sarantopoulos A, Lefaki I, Skendros P, Papadopoulos P. Eosinophilic cellulitis (Wells' syndrome) as a cutaneous reaction to the administration of adalimumab. *Ann Rheum Dis* **65**: 839-840, 2006.
9. Cancelliere N, Barranco P, Vidaurázaga C, Benito DM, Quirce S. Subacute prurigo and eosinophilia in a patient with rheumatoid arthritis receiving infliximab and etanercept. *J Investig Allergol Clin Immunol* **21**: 248-249, 2011.
10. Malisiewicz B, Murer C, Pachlopnik Schmid J, French LE, Schmid-Grendelmeier P, Navarini AA. Eosinophilia during psoriasis treatment with TNF antagonists. *Dermatology* **223**: 311-315, 2011.
11. Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Van Assche G. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. *Aliment Pharmacol Ther* **36**: 312-323, 2012.
12. Tugnet N, Youssef A, Whallett AJ. Wells' syndrome (eosinophilic cellulitis) secondary to infliximab. *Rheumatology (Oxford)* **51**: 195-196, 2012.
13. Vester K, Rüger RD, Harth W, Simon JC. Transient blood eosinophilia during treatment with Adalimumab. *J Eur Acad Dermatol Venereol* **26**: 924-925, 2012.
14. Adamson R, Yazici Y, Katz ES, Greisman SG, Steiger D. Fatal acute necrotizing eosinophilic myocarditis temporally related to use of adalimumab in a patient with relapsing polycondritis. *J Clin Rheumatol* **19**: 386-389, 2013.
15. Guidelli GM, Tenti S, Fioravanti A. Severe eosinophilia during anti-tumor necrosis factor-alpha therapy for psoriatic arthritis. *Indian J Dermatol Venereol Leprol* **80**: 187-189, 2014.
16. Nakahigashi K, Egawa G, Miyachi Y, Kabashima K. Digital vasculitis with eosinophilia possibly associated with etanercept therapy. *Acta Derm Venereol* **94**: 239-240, 2014.
17. Honda M, Kuwatsuka Y, Yoshimi K, Tomimura S, Hori M, Utani A. A case of eosinophilic granulomatosis with polyangiitis initially presenting with edematous erythema. *Nishinon J Dermatol* **77**: 115-118, 2015 (in Japanese, Abstract in English).
18. Morrisroe K, Wong M. Drug-induced hypereosinophilia related to tocilizumab therapy for rheumatoid arthritis. *Rheumatology (Oxford)* **54**: 2113-2114, 2015.
19. Chiriac A, Brzezinski P, Stolnicu S, et al. Eosinophilia - A rare possible adverse reaction during anti-tumor necrosis factor-alpha therapy for psoriasis. *J Dermatolog Treat* **27**: 110-113, 2016.
20. Shelley WB, Talanin N, Shelley ED. Polysorbate 80 hypersensitivity. *Lancet* **345**: 1312-1313, 1995.
21. Coors EA, Seybold H, Merk HF, Mahler V. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Ann Allergy Asthma Immunol* **95**: 593-599, 2005.
22. Norris LB, Qureshi ZP, Bookstaver PB, et al. Polysorbate 80 hypersensitivity reactions: a renewed call to action. *Commun Oncol* **7**: 425-428, 2010.
23. Pérez-Pérez L, García-Gavín J, Piñeiro B, Zulaica A. Biologic-induced urticaria due to polysorbate 80: usefulness of prick test. *Br J Dermatol* **164**: 1119-1120, 2011.
24. Vultaggio A, Nencini F, Pratesi S, Petroni G, Maggi E, Matucci A. Manifestations of antidrug antibodies response: hypersensitivity and infusion reactions. *J Interferon Cytokine Res* **34**: 946-952, 2014.
25. Vultaggio A, Matucci A, Nencini F, Pratesi S, Maggi E. Hypersensitivity reactions to biologicals: True allergy?. *Curr Treat Options Allergy* **3**: 147-157, 2016.
26. Puxeddu I, Caltran E, Rocchi V, Del Corso I, Tavoni A, Migliorini P. Hypersensitivity reactions during treatment with biological agents. *Clin Exp Rheumatol* **34**: 129-132, 2016.
27. van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* **9**: 164-172, 2013.
28. Keiserman M, Codreanu C, Handa R, et al. The effect of antidrug antibodies on the sustainable efficacy of biologic therapies in rheumatoid arthritis: practical consequences. *Expert Rev Clin Immunol* **10**: 1049-1057, 2014.
29. Thomas SS, Borazan N, Barroso N, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. A systematic review and meta-analysis. *BioDrugs* **29**: 241-258, 2015.
30. Ogata A, Tanimura K, Sugimoto T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* **66**: 344-354, 2014.
31. Haggerty HG, Abbott MA, Reilly TP, et al. Evaluation of immunogenicity of the T cell costimulation modulator abatacept in patients treated for rheumatoid arthritis. *J Rheumatol* **34**: 2365-2373, 2007.
32. Nash P, Nayiager S, Genovese MC, et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study. *Arthritis Care Res (Hoboken)* **65**: 718-728, 2013.
33. Interview form for Actemra tocilizumab 80 mg, 200 mg and 400 mg for intravenous drip infusion. [Internet]. [cited 2016 Aug 5]. Available from: http://chugai-pharm.jp/hc/di/scholar/item/drug_dat/a/act/if/act_if.pdf
34. Tanaka Y, Harigai M, Takeuchi T, et al. Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. *Mod Rheumatol* **26**: 481-489, 2016.
35. Interview form for Simponi golimumab 50 mg for subcutaneous injection. [Internet]. [cited 2016 Sept 18]. Available from: http://medical.mt-pharma.co.jp/di/file/if/f_smp_a.pdf
36. Lonberg N. Fully antibodies from transgenic mouse and phage display platforms. *Curr Opin Immunol* **20**: 450-459, 2008.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).