Review Article

Advances in the Treatment of Rheumatoid Arthritis

Eisuke Tanaka[1)] Sei Muraoka[2)]* and Toshihiro Nanki[2)]

[1)]Medical Student, Toho University School of Medicine, Tokyo, Japan
[2)]Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, Tokyo, Japan

ABSTRACT: Rheumatoid arthritis (RA) is characterized by synovitis, bone erosion, and cartilage destruction, which ultimately lead to joint destruction. The pyramidal plan, which aims to attenuate symptoms, was the standard treatment for RA. However, advances in therapeutic agents mean that the maintenance of remission is now a realistic treatment goal. Recent treatments, including methotrexate, biological disease-modifying anti-rheumatic drugs, and Janus kinase inhibitors, achieve low disease activity and improve the prognosis of RA; however, not all patients exhibit favorable responses. Furthermore, the economic burden and adverse effects associated with these treatments have not yet been resolved. Therefore, the development of more effective and safer therapies is required. Advances in the treatment of RA have been discussed herein.

Toho J Med 7 (1): 1–10, 2021

KEYWORDS: biologics, Janus kinase inhibitors, methotrexate, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that is characterized by polyarthritis. Prolonged synovitis leads to joint destruction and decreases in the activities of daily living.[1)] The progression of joint destruction is marked in the first 2 years of RA.[2)] Therapeutic interventions may restore the quality of life of patients with early RA to that of a healthy population but not that of established RA with bone destruction, even if remission is achieved.[3)] Therefore, the early diagnosis and treatment initiation for RA are crucial. The new classification criteria advocated in 2010 by the American College of Rheumatology/The European League Against Rheumatism (ACR/EULAR) contribute to the early diagnosis of RA.[4)] Furthermore, a strategy of intensive treatment with the defined goals of achieving low disease activity (LDA), reducing bone destruction, and restoring physical function has been established.[5)] Therefore, the concept of treat to target (T2T), the aim of which is remission through early diagnosis and treatment, has become the standard of care.[6)]

History

Conventional RA treatment, called the pyramidal plan, had been focused on short-term relief of joint symptoms, starting with patient education, exercise, and rest, and drug therapies were initiated with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and intraarticular injections or oral glucocorticoids (GC). After the above treatments were attempted, experimental treatments need to be considered.[7)] Although GC exert anti-inflammatory effects and inhibit bone destruction, their adverse effects, including infections, such as pneumonia,[8)] and osteoporosis,[9)] have not yet been resolved. Therefore, the dosage of GC administered needs to be minimized. Regarding DMARDs, in-

*Corresponding Author: Sei Muraoka, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan, tel: +81–3–762–4151
e-mail: seimuraoka@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2020-009

Received May 8, 2020: Accepted June 22, 2020
Toho Journal of Medicine 7 (1), Mar. 1, 2021.
ISSN 2189–1990, CODEN: TJMOA2

Table 1 Classification of disease-modifying anti-rheumatic drugs (DMARDs)

Synthetic DMARDs (sDMARDs)		Biological DMARDs (bDMARDs)	
Conventional synthetic	Targeted synthetic	Biological originator	Biosimilar
methotrexate	tofacitinib	infliximab	infliximab BS
salazosulfapyridine	baricitinib	adalimumab	etanercept BS
leflunomide	peficitinib	golimumab	
bucillamine		etanercept	
iguratimod		certolizumab pegol	
auranofin		tocilizumab	
sodium aurothiomalate		sarilumab	
actarit		abatacept	
mizoribine			
tacrolimus			

jectable gold, salazosulfapyridine, and bucillamine were commonly used in the treatment of RA.

Methotrexate (MTX) is a highly effective treatment for RA that was approved in the United States in 1989 and Japan in 1999. It is currently the first-line anchor drug for RA. Biological DMARDs (bDMARDs) were introduced in 1998 and exerted their effects by suppressing targeted inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin (IL)-6, or modulating T cell costimulatory molecules. Since the emergence of DMARDs, the concept of T2T became the standard of care for RA.[6] The aim of T2T is remission and the prevention of radiographic progression, leading to a good life expectancy. A previous study reported that the survival of RA patients in the UK was better in 2007-2014 than in 1999-2006, and this was attributed to advances in diagnosis and treatment.[10] Moreover, a cohort with a strong therapeutic strategy, namely, the targeting of LDA patients in the Netherlands, showed that intensive treatment reduced disease activity and functional deterioration, and the survival of these patients was similar to that of the general population.[11] Due to recent advances in therapies, orthopedic surgery is less frequently indicated for RA patients.[12]

Treatment

RA treatments are divided into two categories: synthetic DMARDs (sDMARDs) and bDMARDs. sDMARDs are subdivided into conventional sDMARDs (csDMARDs) and targeted sDMARDs (tsDMARDs). csDMARDs are traditional low-molecular-weight compounds, such as MTX, and Janus kinase (JAK) inhibitors are categorized as tsDMARDs. bDMARDs are also subdivided into biological originator DMARDs (boDMARDs) and biosimilar DMARDs (bsDMARDs)[13] (Table 1). Treatment recommendations for RA involve strategies aimed at remission or LDA with the administration of csDMARDs centered on MTX and the use of bDMARDs and JAK inhibitors for patients who do not respond to MTX.[14, 15]

MTX

MTX is a folic acid antagonist that inhibits the proliferation of malignant cells by suppressing the synthesis of purines and pyrimidines, and was initially introduced for the treatment of pediatric acute leukemia. MTX was used to treat RA for the first time in the 1950s. MTX is a cost-effective approach and the anchor drug for RA. The effectiveness of MTX was confirmed by a Cochrane review of 14 papers on MTX reported from 1966 to 2013. It concluded that the efficacy of 5-25 mg/week MTX was clinically evident and significant as a short-term treatment (12-52 weeks).[16] MTX monotherapy achieves equivalent efficacy to TNF inhibitor monotherapy, and the concomitant use of bDMARDs with MTX was found to be more effective than MTX monotherapy.[17] The relationship between the dose and efficacy of MTX has been extensively examined. The average dose of MTX was shown to correlate with LDA.[18] However, when used in combination with certolizumab pegol (CZP), an anti-TNF monoclonal antibody (mAb), the dose-dependent inhibitory effects of MTX on joint damage were not observed.[19] In addition, no significant differences were noted in efficacy or anti-drug antibody production rates between MTX at 10 mg/week and 20 mg/week in combination with adalimumab (ADA), another anti-TNF mAb; however, adverse effects were more frequent at 20 mg/week.[20] Based on these findings, the Japanese guidelines for the use of MTX recommend a dose of 10-12 mg/week.[21]

Table 2 The efficacy of concomitant use of MTX with molecular-targeted therapies

	DAS28 remission rate (%) at week 52	
	Combination with MTX	Monotherapy
ETA (25 mg×2/week)	35.6	18.8
ADA (40 mg/2 weeks)	43	23
ABT (125 mg/week)	61.3	45.7
TCZ (8 mg/kg/4 weeks)	week 24: 69.6 → week 52: 72.2	week 24: 55.0 → week 52: 70.3
TOF (5 mg twice daily)	15	11

ABT, abatacept; ADA, adalimumab; DAS, disease activity score; ETA, etanercept; MTX, methotrexate; TCZ, tocilizumab; TOF, tofacitinib

bDMARDs

TNF inhibitors

TNF inhibitors exhibit their efficacy by neutralizing the bioactivity of TNF. Five types of TNF inhibitors are currently available in Japan and exert similar therapeutic effects, which are enhanced when used in combination with MTX. MTX monotherapy reduces disease activity to a similar extent as TNF inhibitor monotherapy; however, TNF inhibitors prevent joint destruction even in patients with poor clinical benefit.[22] The usefulness of TNF inhibitors for RA was demonstrated in large-scale clinical studies; however, 30%-50% of patients were primary or secondary failures for TNF inhibitors at long-term observations.[23] All TNF inhibitors were similarly effective in MTX-naive, MTX-refractory, and TNF inhibitor-refractory cases.[24] Therefore, the individualized selection of TNF inhibitors for each patient is recommended based on the characteristics of each drug.

Etanercept (ETA)

TNF inhibitors are classified into receptor and antibody formulations based on their structures, with the former only including ETA. ETA is the first TNF inhibitor to be marketed for the treatment of RA. The clinical remission rate of the combination of ETA and MTX was 50%, which was significantly higher than that of MTX monotherapy (28%).[25] Furthermore, structural remission with the combination of ETA and MTX was superior to that with MTX monotherapy. This combination was also shown to maintain its efficacy for 3 years.[17] ETA has a higher remission rate when combined with MTX as compared to ETA monotherapy (Table 2).[26] The low immunogenicity of ETA makes it suitable for long-term use. Collectively, these findings demonstrated the usefulness of the combination of MTX and TNF inhibitors.[25] However, remission rates did not significantly differ between the group that continued the combination of ETA and MTX and the group that continued ETA alone after using ETA plus MTX (45% and 37%, respectively).[27] ETA monotherapy suppressed bone destruction more effectively than MTX monotherapy in high disease activity patients.[17] Additionally, the concentration of ETA in maternal cord blood after its administration was as low as 3.6%, and it was not detected in infant blood 12 weeks after birth.[28] Therefore, ETA may be administered during pregnancy depending on the patient's situation.

Infliximab (IFX)

IFX is the first anti-TNF mAb used for RA patients. IFX plus MTX suppressed not only disease activity but also joint destruction for RA patients who did not respond to MTX.[29] IFX is a chimeric anti-human TNF mAb. Human anti-chimeric Ab (HACA) was produced following the administration of IFX alone, which reduced its clinical effects; however, the concomitant use of MTX inhibited HACA production.[30] One of the factors inducing the production of human anti-chimeric Abs is a low blood concentration of IFX.[31] Therefore, the efficacy of IFX is dependent on its trough serum level, and the maintenance of a trough serum level of 1 μg/mL or higher increased EULAR response rates to moderate or good responses.[32] Furthermore, treatment with 10 mg/kg IFX enhanced its efficacy without increasing the risk of adverse effects. Based on these findings, a low blood concentration of IFX promotes the production of anti-drug Ab, and increases in the dose administered represent an effective therapeutic method.[32]

ADA

ADA is a fully human anti-TNF mAb. The immunogenicity of ADA is weaker than that of IFX; however, the concomitant use of MTX is desirable from the perspective of efficacy and immunogenicity. ADA showed high clinical efficacy in MTX-refractory cases, and the combination of ADA and MTX for 1 year suppressed joint destruction.[33]

In early MTX-naive RA patients, the combination of ADA and MTX reduced disease activity and bone destruction more effectively than ADA monotherapy (Table 2).[34] Regarding the optimal dose of MTX in combination with ADA, the efficacies of 10 mg/week and 20 mg/week of MTX were similar in early RA patients.[20] The establishment of an optimal dose of MTX is important for increasing efficacy and reducing the risk of adverse effects when it is administered in combination with TNF inhibitors.

Golimumab (GLM)

GLM is also a fully human mAb against TNF. Combination therapy with GLM and MTX was found to be as effective as other bDMARDs in patients with insufficient responses to MTX.[35] GLM is produced by human immunoglobulin transgenic mice immunized with TNF and is characterized by its low immunogenicity. The positive rate of the anti-GLM antibody is approximately 5%, even without MTX, and its long-term administration is possible.[36] Although GLM monotherapy is less effective than its concomitant use with MTX, it represents a treatment option for RA due to its low immunogenicity.

CZP

CZP consists of the Fab' fragment of humanized anti-TNF mAb linked to polyethylene glycol. Since CZP lacks Fc, its placental transfer is low and its transfer into infants[37] and breast milk[38] is minimal. CZP is characterized by low immunogenicity because of the absence of Fc. The administration of CZP with a loading-dose strategy was previously shown to achieve clinical efficacy within 2 weeks.[39] Furthermore, the administration of CZP plus MTX to RA patients with an inadequate response to MTX resulted in superior remission rates to those with MTX alone by week 24 (58.8% *vs.* 13.6%, respectively).[40] CZP plus MTX was also shown to be as effective as ADA plus MTX.[41]

Inhibitor of T Cell Costimulation

Abatacept (ABT)

ABT is a soluble fusion protein composed of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the Fc domain of IgG1, and inhibits CD28-mediated costimulatory signals by binding to CD80/CD86 on antigen-presenting cell surfaces. Consequently, ABT suppresses the activation of T cells and inhibits the production of inflammatory cytokines and mediators. The disease activity score 28 remission rate of ABT plus MTX was superior to that of MTX monotherapy (60.9% *vs.* 45.2%, respectively) and TNF inhibitors.[42] In addition, the clinical efficacy of combination therapy of ABT and MTX was demonstrated in patients with insufficient responses to MTX and TNF inhibitors.[43, 44] ABT has a higher remission rate when combined with MTX compared with ABT monotherapy (Table 2).[45] Moreover, ABT plus MTX was as effective as ADA plus MTX in bDMARD-naive RA patients who were refractory to MTX, and the frequency of severe adverse effects and discontinuation was lower in ABT plus MTX.[46] ABT and tocilizumab (TCZ), an anti-IL6 receptor mAb, exerted similar clinical effects in a study based on propensity score matching; [47] ABT was as effective as other bDMARDs, and since the production of neutralizing antibodies in response to ABT was limited, it maintained its therapeutic effects. Anti-cyclic citrullinated peptide antibody-positive RA patients showed better responses to ABT and had a higher persistence rate.[48] Furthermore, ABT was safely administered to RA patients with interstitial pneumonia.[49] Moreover, its efficacy does not depend on body weight.[50] Thus, ABT is advantageous for RA patients with comorbidities.

IL-6 receptor antagonists

IL-6 is a cytokine that induces the production of platelets, inflammation, the activation of osteoclasts, and angiogenesis. TCZ and sarilumab (SAR) are anti-IL-6 receptor mAb formulations that both exert IL-6 inhibitory effects. They show superior persistence rates due to the low production of neutralizing antibodies.

TCZ

TCZ is a humanized anti-human IL-6 receptor mAb. TCZ is effective for RA patients who do not respond to MTX or TNF inhibitors.[51] Although the efficacy of TNF inhibitors was not significantly different from that of MTX monotherapy, TCZ monotherapy was shown to be more effective than MTX monotherapy.[52] Although the remission rate is higher in TCZ plus MTX group than TCZ monotherapy at weeks 24 from the start of the study, those two groups became equivalent at weeks 52.[53] From these, the combination of MTX is less effective in TCZ (Table 2). The efficacy of TCZ monotherapy in MTX-refractory patients was significantly greater than that of ADA monotherapy.[54] Therefore, TCZ is recommended for patients who cannot use csDMARDs, such as MTX.[15] However, the concomitant use of MTX may still be effective. Long-term observations revealed that the combination of TCZ and MTX significantly suppressed bone destruction (92.8% *vs.* 86.1%, $p = 0.016$) and achieved a higher remission rate (45.5% *vs.* 36.6%, $p = 0.03$) than TCZ mono-

therapy.[55] Therefore, combination therapy with the concomitant use of MTX as well as other TNF inhibitors represents an effective treatment for RA. Although a subcutaneous TCZ injection is generally administered once every 2 weeks, weekly administration is recommended for intractable cases.[56]

SAR

SAR has recently been approved for the treatment of RA. It is the first fully human mAb against the IL-6 receptor α subunit and is characterized by the maintenance of high serum drug concentrations. SAR exhibited efficacy in RA patients with insufficient responses to MTX.[57] ACR20 response rate of SAR in TNF inhibitors refractory patients at week 24 was 60.9% in patients treated with 200 mg biweekly and 55.8% in those with 150 mg biweekly. These response rates were both significantly higher than those by patients who received a placebo (33.7%). These findings indicate that SAR is a treatment option for RA patients who are refractory to TNF inhibitors.[58] In addition, the efficacy of SAR monotherapy was superior to that of ADA monotherapy in 369 RA patients with high disease activity and inadequate responses to MTX.[59] Therefore, SAR monotherapy is expected to be as effective as TCZ monotherapy.

JAK inhibitors

The JAK/signal transducer and activator of transcription pathway is one of the intracellular signaling pathways of cytokine receptors and is involved in cell proliferation and differentiation. JAK inhibitors are small molecules that exert anti-rheumatic effects by reducing the production of a number of inflammatory cytokines, which play an important role in RA.[60] These inhibitors are characterized by their oral route of administration and do not induce the production of anti-drug antibodies. Three JAK inhibitors are currently available in Japan: tofacitinib (TOF), which mainly inhibits JAK1/3, baricitinib (BAR), which mostly inhibits JAK1/2, and peficitinib, a recently launched pan-JAK inhibitor.[61] Furthermore, upadacitinib and filgotinib are currently being developed; therefore, the choice of JAK inhibitors is expanding.

TOF is the most commonly used JAK inhibitor. The efficacy of TOF monotherapy was shown to be superior to that of MTX monotherapy in MTX-naive RA patients,[62] and it was also effective in patients with insufficient responses to csDMARDs[63] and bDMARDs.[64] TOF has a higher remission rate when combined with MTX compared with TOF monotherapy (Table 2).[65] In addition, TOF plus MTX was as effective as ADA plus MTX in patients with insufficient responses to MTX.[65]

BAR is excreted by the kidneys, whereas TOF is mainly metabolized in the liver. Previous studies reported that BAR showed similar efficacy to TOF in patients with insufficient responses to MTX[66] and TNF inhibitors.[67] Moreover, in patients with insufficient responses to MTX, BAR was as effective as ADA.[68] These findings demonstrated that the efficacy of BAR was equal or superior to bDMARDs, and it remained highly effective even when administered without MTX.[15]

Discontinuation of bDMARDs

The following clinical trials indicated the possibility of dose reductions in or the discontinuation of bDMARDs. IFX was discontinued by RA patients after achieving LDA with IFX plus MTX,[69] with 48% of patients subsequently relapsing. The study,[70] which investigated the withdrawal of ADA without GC or NSAIDs, showed that 48% of patients maintained remission for 52 weeks. The remission rate after drug withdrawal was high in patients achieving deep remission, and all patients who relapsed after drug withdrawal achieved LDA following the re-administration of ADA. The re-administration of other biologics for relapsing patients also reduced disease activity.[71] After achieving LDA with the combination of MTX and ETA, the remission rate in the ETA 50 mg continuation group was 66.7%, whereas that in the ETA 25 mg dose reduction group was 60.2%, and both remission rates were maintained. However, the remission rate in the ETA discontinued group was 29.4%. These findings indicated that although the discontinuation of ETA is not a realistic option, dose reductions are possible.[72] Only 26.2% of RA patients treated with TCZ plus MTX maintained LDA by discontinuing both TCZ and MTX. The re-administration of TCZ was effective in patients with flares after its initial discontinuation.[73] Even if the dose of concomitant MTX was reduced or discontinued at the time of remission in patients with TCZ plus MTX, the control of disease activity was equivalent to that in the group that continued with the same dose of MTX.[74, 75] These findings suggest the potential for dose reductions in or the discontinuation of MTX in stable patients treated with TCZ.

Based on these findings, the appropriateness of dose reductions or discontinuation needs to be carefully considered for patients who achieve deep remission.

Infection as an Adverse Event

A previous study conducted in the United States showed that the susceptibility of RA patients to infections was 1.8-fold higher than that of healthy individuals following the elimination of confounding factors.[76] Older age, the use of GC, and high disease activity increased susceptibility to infections.[77] Although the suppression of RA disease activity reduces the frequency of infection, the immunosuppressive effects of various DMARDs may increase susceptibility.

The influence of MTX on the frequency of infection has been extensively examined. Although several reports showed an increase in the frequency of infections by MTX, the general opinion is that it does not increase the incidence of infections.[78]

The risk of serious infections was previously shown to be 2-fold higher in RA patients treated with TNF inhibitors than in those administered non-bDMARDs.[79] The administration of ADA and IFX slightly increased the risk of serious infection, whereas ETA exerted the opposite effects.[80] Previous studies investigated the risk factors for serious infections in patients with bDMARDs and identified the following: the use of GC, older age, existing lung diseases, physical disability, and diabetes mellitus (DM).[81, 82] Harigai et al. reported that RA patients with any two of the following three risk factors were at risk of developing *Pneumocystis* pneumonia during IFX therapy: 65 years or older, prednisolone 6 mg/day or more, and existing lung diseases.[83] Moreover, the incidence of tuberculosis increased in RA patients treated with TNF inhibitors[84] but was lower with ETA than with antibody formulations.[85] Nevertheless, the importance of adequate tuberculosis screening and the preventive administration of isoniazid is the same for any formulations, including ETA.

Regarding IL-6 receptor inhibitors, a similar frequency of infection was reported for SAR and TCZ,[86] whereas no significant differences were observed between TCZ and other bDMARDs.[87] The following risk factors were associated with the development of serious infections during TCZ therapy: 65 years or older, disease duration of 10 years or more, previous or concurrent respiratory disease, and prednisolone 5 mg/day or more, with the risk of infection being higher in patients with more of these risk factors.[88] Since increases in the levels of C-reactive protein, a sign of infection, may not be observed in patients treated with IL-6 receptor inhibitors, careful examinations are needed to prevent the delayed detection of infectious diseases.

Among bDMARDS, ABT is associated with a lower risk of severe infections,[89] which is reflected in the British Society for Rheumatology guidelines, similar to ETA.[90]

The risk of serious infection with TOF is similar to that with bDMARDs,[91] and risk factors include older age, the presence of chronic obstructive pulmonary disease, the use of GC, a low score on a health assessment questionnaire, lymphocyte count less than 500/μL, and DM.[92] Careful monitoring for the appearance of herpes zoster is also important in high-risk patients, such as the elderly, those treated with GC, and Asians.[93]

In summary, the risks of infection associated with each DMARD are similar. However, ABT and ETA are preferentially administered to high-risk patients. Dose reductions in GC may lower the risk of infection and suppress disease activity through the optimal use of bDMARDs and JAK inhibitors.

Future Treatments

Although the prognosis of RA patients was previously reported to be 10 years shorter than the general population, it has been improving in recent years because of the better control of disease activity with newly developed treatments, such as bDMARDs and tsDMARDs.[94] However, the economic burden of these treatments remains unresolved. Biosimilar agents have recently become available and exhibited equivalent efficacy and safety in clinical trials. These agents are now used worldwide and are expected to reduce this economic burden.[95]

Some patients do not achieve LDA with currently available treatments. Moreover, increases in the frequencies of infections are a cause for concern. Therefore, the development of safer drugs is urgently needed. Several new candidates are undergoing clinical trials, such as anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies[96] and adenosine A3 receptor inhibitors.[97] Fractalkine (FKN), a type of chemokine, has been attracting increasing attention as a new therapeutic target molecule for RA.[98] FKN and its receptor, CX3CR1, are expressed in RA synovial tissue.[98] An anti-FKN mAb was shown to ameliorate arthritis in collagen-induced arthritis mice.[98] Furthermore, a phase 1/2 trial demonstrated the safety and tolerability as well as clinical efficacy of an anti-FKN mAb in active RA patients for 12 weeks.[99]

Conclusion

Prognosis of RA patients has extensively improved by advanced treatment, including MTX, bDMARDs, and tsDMARDs. We need to choose appropriate therapy for each patient and also consider risk, such as infection.

Disclaimer: Toshihiro Nanki is one of the Editors of Toho Journal of Medicine. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Conflicts of interest: Toshihiro Nanki received research supports from: Bristol-Myers K.K., Asahikasei Pharma Corp., and KAN Research Institute, Inc, Consultant of: Chugai Pharmaceutical Co., Scholarships or other donations: Mitsubishi-Tanabe Pharma Co., Chugai Pharmaceutical Co., Eisai Co., Ltd., Bayer Yakuhin, Ltd., Ayumi Pharmaceutical Co., Asahikasei Pharma Corp., and AbbVie GK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

1) Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018; 4: 18001.
2) Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol. 1989; 16: 585-91.
3) Scott IC, Ibrahim F, Lewis CM, Scott DL, Strand V. Impact of intensive treatment and remission on health-related quality of life in early and established rheumatoid arthritis. RMD Open. 2016; 2: e000270.
4) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010; 62: 2569-81.
5) Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004; 364: 263-9.
6) Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016; 75: 3-15.
7) Smyth CJ. Therapy of rheumatoid arthritis. A pyramidal plan. Postgrad Med. 1972; 51: 31-9.
8) Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006; 54: 628-34.
9) van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002; 13: 777-87.
10) Zhang Y, Lu N, Peloquin C, Dubreuil M, Neogi T, Avina-Zubieta JA, et al. Improved survival in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis. 2017; 76: 408-13.
11) Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YP, van Groenendael JH, Han KH, et al. Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial. Ann Intern Med. 2016; 164: 523-31.
12) Momohara S, Ikari K, Kawakami K, Iwamoto T, Inoue E, Yano K, et al. The increasing disease duration of patients at the time of orthopaedic surgery for rheumatoid arthritis. Rheumatol Int. 2012; 32: 3323-4.
13) Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014; 73: 3-5.
14) Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016; 68: 1-26.
15) Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020.
16) Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2014; CD000957.
17) van der Heijde D, Klareskog L, Landewe R, Bruyn GA, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007; 56: 3928-39.
18) Yamanaka H, Inoue E, Tanaka E, Nakajima A, Taniguchi A, Terai C, et al. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). Mod Rheumatol. 2007; 17: 98-105.
19) Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016; 75: 75-83.
20) Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis. 2015; 74: 1037-44.
21) Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, et al. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. Mod Rheumatol. 2019; 29: 31-40.
22) Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from

the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum. 2005; 52: 1020-30.
23) Caporali R, Crepaldi G, Codullo V, Benaglio F, Monti S, Todoerti M, et al. 20 years of experience with tumour necrosis factor inhibitors: what have we learned? Rheumatology (Oxford). 2018; 57: vii5-10.
24) Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol. 2015; 11: 276-89.
25) Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008; 372: 375-82.
26) Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol. 2011; 38: 1585-92.
27) Emery P, Breedveld F, van der Heijde D, Ferraccioli G, Dougados M, Robertson D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. 2010; 62: 674-82.
28) Murashima A, Watanabe N, Ozawa N, Saito H, Yamaguchi K. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. Ann Rheum Dis. 2009; 68: 1793-4.
29) Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group Lancet. 1999; 354: 1932-9.
30) Schaeverbeke T, Truchetet ME, Kostine M, Barnetche T, Bannwarth B, Richez C. Immunogenicity of biologic agents in rheumatoid arthritis patients: lessons for clinical practice. Rheumatology (Oxford). 2016; 55: 210-20.
31) Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology (Oxford). 2007; 46: 1828-34.
32) Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol. 2009; 19: 478-87.
33) Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004; 50: 1400-11.
34) Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006; 54: 26-37.
35) Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009; 68: 789-96.
36) Takeuchi T, Harigai M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, et al. Clinical efficacy, radiographic, and safety results of golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior therapy with disease-modifying antirheumatic drugs: Final results of the GO-MONO trial through week 120. Mod Rheumatol. 2018; 28: 770-9.
37) Mariette X, Forger F, Abraham B, Flynn AD, Molto A, Flipo RM, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018; 77: 228-33.
38) Clowse ME, Forger F, Hwang C, Thorp J, Dolhain RJ, van Tubergen A, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017; 76: 1890-6.
39) Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014; 24: 715-24.
40) Keystone E, Heijde D, Mason D Jr, Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008; 58: 3319-29.
41) Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet. 2016; 388: 2763-74.
42) Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barre E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis. 2015; 74: 19-26.
43) Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006; 144: 865-76.
44) Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005; 353: 1114-23.
45) Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barré E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis. 2015; 74: 19-26.
46) Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G,

Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014; 73: 86-94.
47) Kubo S, Nakayamada S, Nakano K, Hirata S, Fukuyo S, Miyagawa I, et al. Comparison of the efficacies of abatacept and tocilizumab in patients with rheumatoid arthritis by propensity score matching. Ann Rheum Dis. 2016; 75: 1321-7.
48) Alten R, Nusslein HG, Mariette X, Galeazzi M, Lorenz HM, Cantagrel A, et al. Baseline autoantibodies preferentially impact abatacept efficacy in patients with rheumatoid arthritis who are biologic naive: 6-month results from a real-world, international, prospective study. RMD Open. 2017; 3: e000345.
49) Fernandez-Diaz C, Loricera J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum. 2018; 48: 22-7.
50) Schafer M, Meissner Y, Kekow J, Berger S, Remstedt S, Manger B, et al. Obesity reduces the real-world effectiveness of cytokine-targeted but not cell-targeted disease-modifying agents in rheumatoid arthritis. Rheumatology (Oxford). 2019.
51) Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006; 54: 2817-29.
52) Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010; 69: 88-96.
53) Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Ann Rheum Dis. 2016; 75: 1917-23.
54) Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013; 381: 1541-50.
55) Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis. 2014; 73: 803-9.
56) Abdallah H, Hsu JC, Lu P, Fettner S, Zhang X, Douglass W, et al. Pharmacokinetic and Pharmacodynamic Analysis of Subcutaneous Tocilizumab in Patients With Rheumatoid Arthritis From 2 Randomized, Controlled Trials: SUMMACTA and BREVACTA. J Clin Pharmacol. 2017; 57: 459-68.
57) Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015; 67: 1424-37.
58) Fleischmann R, van Adelsberg J, Lin Y, Castelar-Pinheiro GD, Brzezicki J, Hrycaj P, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017; 69: 277-90.
59) Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017; 76: 840-7.
60) Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017; 13: 234-43.
61) Kivitz AJ, Gutierrez-Urena SR, Poiley J, Genovese MC, Kristy R, Shay K, et al. Peficitinib, a JAK Inhibitor, in the Treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. Arthritis Rheumatol. 2017; 69: 709-19.
62) Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014; 370: 2377-86.
63) Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012; 367: 495-507.
64) Charles-Schoeman C, Burmester G, Nash P, Zerbini CA, Soma K, Kwok K, et al. Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2016; 75: 1293-301.
65) Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017; 390: 457-68.
66) Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015; 74: 333-40.
67) Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016; 374: 1243-52.
68) Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017; 376: 652-62.
69) van den Broek M, Klarenbeek NB, Dirven L, van Schaardenburg D, Hulsmans HM, Kerstens PJ, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. Ann Rheum Dis. 2011; 70: 1389-94.
70) Tanaka Y, Hirata S, Kubo S, Fukuyo S, Hanami K, Sawamukai N, et al. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. Ann Rheum Dis. 2015; 74: 389-95.
71) Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Maldonado MA, et al. Re-treatment with abatacept plus methotrexate for disease flare after complete treatment withdrawal in patients with early rheumatoid arthritis: 2-year results from the AVERT study. RMD Open. 2019; 5: e000840.

72) Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013; 381: 918-29.
73) Nishimoto N, Amano K, Hirabayashi Y, Horiuchi T, Ishii T, Iwahashi M, et al. Retreatment efficacy and safety of tocilizumab in patients with rheumatoid arthritis in recurrence (RESTORE) study. Mod Rheumatol. 2014; 24: 26-32.
74) Edwards CJ, Ostor AJK, Naisbett-Groet B, Kiely P. Tapering versus steady-state methotrexate in combination with tocilizumab for rheumatoid arthritis: a randomized, double-blind trial. Rheumatology (Oxford). 2018; 57: 84-91.
75) Kremer JM, Rigby W, Singer NG, Birchwood C, Gill D, Reiss W, et al. Sustained response following discontinuation of methotrexate in patients with rheumatoid arthritis treated with subcutaneous tocilizumab: results from a randomized, controlled trial. Arthritis Rheumatol. 2018; 70: 1200-8.
76) Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002; 46: 2287-93.
77) Caporali R, Caprioli M, Bobbio-Pallavicini F, Montecucco C. DMARDS and infections in rheumatoid arthritis. Autoimmun Rev. 2008; 8: 139-43.
78) McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L. Methotrexate, rheumatoid arthritis and infection risk: what is the evidence? Rheumatology (Oxford). 2009; 48: 867-71.
79) Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012; 64: 1125-34.
80) Michaud TL, Rho YH, Shamliyan T, Kuntz KM, Choi HK. The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a meta-analysis update of 44 trials. Am J Med. 2014; 127: 1208-32.
81) Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008; 67: 189-94.
82) Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol. 2012; 22: 498-508.
83) Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007; 357: 1874-6.
84) Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001; 345: 1098-104.
85) Ai JW, Zhang S, Ruan QL, Yu YQ, Zhang BY, Liu QH, et al. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-alpha antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. J Rheumatol. 2015; 42: 2229-37.
86) Emery P, Rondon J, Parrino J, Lin Y, Pena-Rossi C, van Hoogstraten H, et al. Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2019; 58: 849-58.
87) Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011; CD008794.
88) Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014; 41: 15-23.
89) Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD, et al. Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in medicare. Arthritis Rheumatol. 2016; 68: 56-66.
90) Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology (Oxford). 2019; 58: e3-e42.
91) Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015; 17: 362.
92) Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis. 2017; 76: 1253-62.
93) Winthrop KL, Curtis JR, Lindsey S, Tanaka Y, Yamaoka K, Valdez H, et al. Herpes Zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. Arthritis Rheumatol. 2017; 69: 1960-8.
94) Lacaille D, Avina-Zubieta JA, Sayre EC, Abrahamowicz M. Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population-closing the mortality gap. Ann Rheum Dis. 2017; 76: 1057-63.
95) Cohen S, Kay J. Biosimilars: implications for rheumatoid arthritis therapy. Curr Opin Rheumatol. 2017; 29: 260-8.
96) Burmester GR, McInnes IB, Kremer J, Miranda P, Korkosz M, Vencovsky J, et al. A randomised phase IIb study of mavrilimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2017; 76: 1020-30.
97) Silverman MH, Strand V, Markovits D, Nahir M, Reitblat T, Molad Y, et al. Clinical evidence for utilization of the A3 adenosine receptor as a target to treat rheumatoid arthritis: data from a phase II clinical trial. J Rheumatol. 2008; 35: 41-8.
98) Nanki T, Imai T, Kawai S. Fractalkine/CX3CL1 in rheumatoid arthritis. Mod Rheumatol. 2017; 27: 392-7.
99) Tanaka Y, Takeuchi T, Umehara H, Nanki T, Yasuda N, Tago F, et al. Safety, pharmacokinetics, and efficacy of E6011, an antifractalkine monoclonal antibody, in a first-in-patient phase 1/2 study on rheumatoid arthritis. Mod Rheumatol. 2018; 28: 58-65.