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INSTRUCTIONAL LECTURE

Treatment of rheumatoid arthritis by molecular-targeted agents: efficacy and limitations

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Abstract Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation due to unknown causes. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and tofacitinib, a targeted sDMARD, can be used to treat RA. In clinical trials, molecular-targeted therapies showed a significant reduction in RA symptoms and provided pain relief for patients with active RA. Even if patients did not show clinical improvement with combination therapy with a bDMARD and methotrexate (MTX), some patients showed a significant inhibition in structural damage. The clinical efficacies of tofacitinib were shown to be equivalent to adalimumab, a bDMARD, in patients with RA treated with MTX. MTX is the first-line agent for the treatment of RA. Higher doses of MTX might be needed to maintain the effects of bDMARDs. Patients receiving some bDMARDs have been shown to have a higher risk for serious infections; thus, pre-screening for infections is important before beginning treatment with bDMARDs. The rates of patients maintaining targeted levels of disease activity after stopping bDMARDs are relatively low. It is uncertain whether remission or low disease activity can be maintained after stopping molecular-targeted therapies. The development of bDMARDs and targeted-molecular sDMARDs has provided a wide range of treatment options for RA. Patients with active RA should be treated with a treat-to-target strategy after assessment of risks and benefits.

Introduction

Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation of unknown cause. Around 1 % of adults are affected by RA worldwide, and the incidence appears to be higher in women. Failure to control active RA induces joint destruction, deformities in the extremities, deterioration of quality of life (QOL), and a high mortality rate [1]. The last decade has witnessed significant developments in the treatment of RA, such as disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), which can reduce the synovial inflammation and partially stop the progression of structural damage. However, although symptomatic improvement and pain relief have been achieved, no therapy appears to prevent disease progression or even disease development. The European League against Rheumatism (EULAR) recommends the use of MTX or combination therapy with a conventional synthetic DMARD (csDMARD) as the first-line therapy for RA as soon as it is diagnosed [2]. Beyond csDMARDs, biological DMARDs (bDMARDs) [3] and tofacitinib [4], a targeted sDMARD (tsDMARD), are available for the treatment of RA. Biological DMARDs and tsDMRADs both have significant advantages and limitations in the treatment of RA. The aim of this paper is to summarize the benefits and drawbacks of these medicines for the treatment of RA for orthopedic surgeons.

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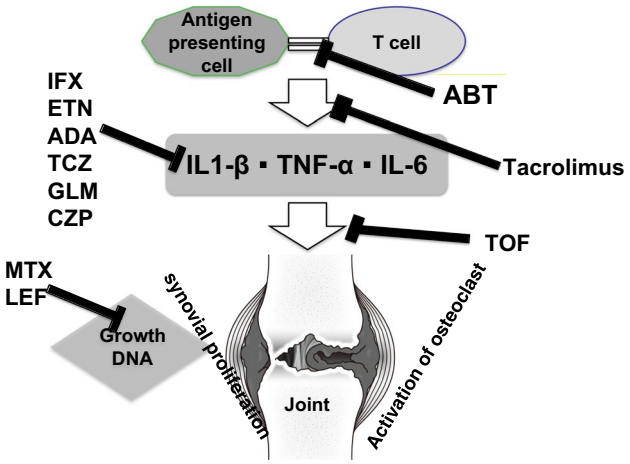

Fig. 1 Critical points blocked by molecular-targeted agents and others in the inflammatory cascade. Each agent blocks the critical points indicated by *rods*. *IFX* infliximab, *ADA* adalimumab, *TCZ* tocilizumab, *ABT* abatacept, *GLM* golimumab, *CZP* certolizumab pegol, *TOF* tofacitinib, *MTX* methotrexate, *LEF* leflunomide, *IL-1β* interleukin-1β, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6

Molecular-targeted medicine

Molecular-targeted therapy is one of the major modalities of medical treatment for cancer. For RA, csDMARDs were developed using an empirical approach without gaining a detailed understanding of their mechanism of action. However, recent developments in science have revealed more information about the inflammatory process that occurs in RA (Fig. 1), making the development of molecular-targeted therapy possible. Patients with RA show higher levels of several cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6. Although the precise role of these cytokines in the pathogenesis of RA is unknown, anti-TNF agents such as infliximab (IFX, monoclonal antibody against TNF-α) [5] or etanercept [ETN, fusion protein of the Fc region of a human immunoglobulin G (IgG) antibody linked to the extracellular portion of the human p75 TNF-receptor, the so-called decoy receptor for TNF] [6] have been shown to lead to dramatic improvement in symptoms of RA and prevent structural damage to the joints. These initial successes with anti-TNF agents in the treatment of RA opened avenues for new strategies with molecular-targeted medicines. Currently approved molecular-targeted medicines in Japan include IFX, ETN, adalimumab (ADA, a fully humanized monoclonal antibody against TNF-α by phage display platform) [7], tocilizumab (TCZ, a humanized anti-human IL-6 receptor antibody of the IgG1 subclass) [8], abatacept (ABT, a T cell-blocking Fc-portion protein of the extracellular domain of CTLA-4) [9], golimumab (GLM, a fully humanized monoclonal antibody against TNF-α by a transgenic mouse platform) [10], certolizumab pegol (CZP, a PEGylated Fc-free monoclonal antibody against TNF-α) [11], and tofacitinib (TOF, an oral Janus kinase inhibitor) [12]. IFX, ETN, ADA, GLM, and CZP are TNF-α inhibitors, and TCZ blocks the activity of IL-6. All of them directly target specific cytokines, whereas ABT decreases the level of cytokines through the inhibition of T-cell communication [13]. TOF interferes with the JAK-STAT intracellular signaling pathway, which mediates the activity of several proinflammatory cytokines. TOF is the only molecular-targeted therapy that can be administered orally.

Effects of molecular-targeted agents

In clinical trials, molecular-targeted agents have been shown to lead to a significant reduction in symptoms and provide pain relief for patients with active RA compared with placebo or MTX alone [6–8, 10, 12, 14–17]. Especially the combination therapy with MTX yielded superior clinical efficacy to monotherapy [5–8, 10–12, 14–19]. The efficacy of some molecular-targeted agents was similar to the efficacy of MTX in the monotherapy setting [14]. Furthermore, these agents are expected to inhibit radiographic progression across all disease activity conditions, whereas joint damage has been shown to progress in patients with low and moderate disease activity levels treated with csDMARDs such as MTX [20]. Even in patients who did not show clinical improvement as evaluated by American College of Rheumatology criteria [21], combination therapy with IFX and MTX provided significant inhibition of structural damage compared with inhibition in patients who received MTX alone [22]. There might be uncoupling of inflammation and joint destruction in RA. Here, the author provided roentgenograms of a case. A 52-year-old female suffering from active rheumatoid arthritis had been treated with IFX and MTX since October 2008. Although she did not show an adequate response to IFX therapy without improvement of DAS, dramatic repair of the proximal interphalangeal (PIP) joint of her right middle finger was observed in May 2009 (Fig. 2a, b).

Clinical efficacy has also been seen with the available bDMARDs compared with placebo. Currently, there is only one head-to-head comparison report on the effects of bDMARDs [9]. In the AMPLE trial [9], subcutaneous ABT and ADA did not show any significant differences in clinical, functional, and radiographic outcomes or adverse events. However, it should be noted that this trial was a randomized controlled trial (RCT) but not conducted in a double-blind fashion. Recently, the clinical efficacies of DMARDs have been estimated based on the improvement of the Disease Activity Score 28 (DAS28) [23]. The DAS28

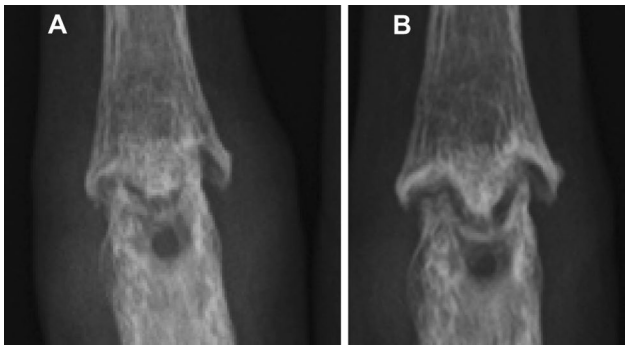

Fig. 2 A case showing radiological repair despite inadequate response to a tumor necrosis factor-α inhibitor. A 52-year-old female suffering from active rheumatoid arthritis had been treated with IFX and MTX since October 2008. Although she did not show an adequate response to IFX therapy without improvement of disease activity, dramatic repair of the proximal interphalangeal (PIP) joint of her right middle finger was observed in May 2009. Roentgenogram of the PIP joints of the right middle finger in October 2008 (**a**) and May 2009 (**b**). *IFX* infliximab, *MTX* methotrexate

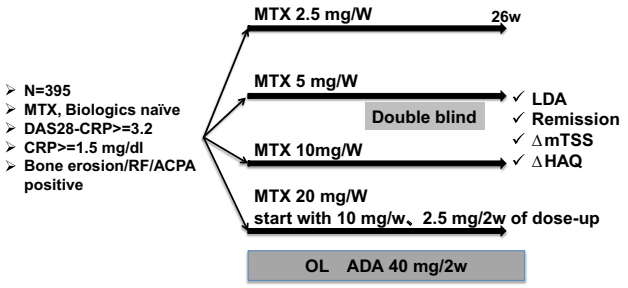

Fig. 3 Schematic protocol of the CONCERTO study. Patients with inclusion criteria for this trial had a disease duration under 1 year, DAS28-CRP ≥3.2, swollen joint count ≥6 of 66 joints assessed, tender joint count ≥8 of 68 joints assessed, CRP ≥1.5 mg/dl or erythrocyte sedimentation rate ≥28 mm/h, and ≥1 bony erosion, RF, or anti-CCP antibody positivity. Patients in the 20 mg/week MTX treatment group were started at 10 mg/week, which was escalated by 2.5 mg every 2 weeks to 20 mg/week by 8 weeks. In case of MTX intolerance/toxicity, blinded MTX dose reduction by 5 mg/week was performed. *MTX* methotrexate, *DAS28* disease activity score 28, *CRP* C-reactive protein, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibody, *LDA* low disease activity, *mTSS* modified total Sharp score, *HAQ* health assessment questionnaire. The author created the figure from the contents of Ref. 30

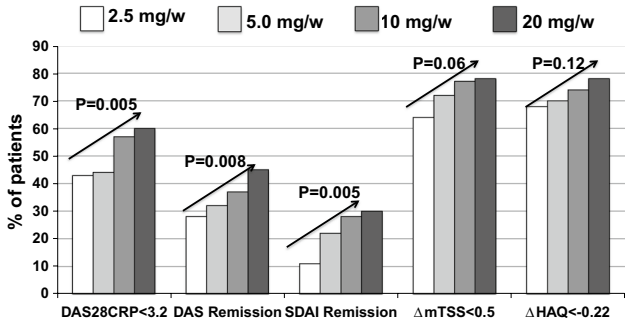

Fig. 4 The effects of increasing doses of MTX on ADA therapy for RA. *DAS28* disease activity score 28, *CRP* C-reactive protein, *SDAI* simplified disease activity index, *mTSS* modified total Sharp score, *HAQ* health assessment questionnaire. The author created the figure from the contents of Ref. 30

consists of four components: tender joint count, swollen joint count, visual analog scale (VAS) score of the patient's global health and laboratory parameters including the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Except for laboratory parameters, the other components are subjective, and the author thinks that caution is required when interpreting the results of a clinical trial that was not performed in a double-blind setting. However, it is a very important result that the joint destruction suppressant effect was the same between those two bDMARDs [9].

All bDMARDs are administered intravenously or subcutaneously mainly because of the difficulty of oral administration by protein preparation. On the other hand, a recently approved small molecule, TOF, is taken orally and might be convenient for patients [4]. TOF was shown to be significantly more effective than placebo, and the clinical efficacies of TOF were equivalent to ADA in patients with RA treated with MTX [12]. Although TOF could provide an effective treatment option for patients with inadequate response to TNF-α inhibitors, such as IFX, ADA, and ETN [18], its safety profile, including the incidence of malignancy and infection by herpes zoster, requires long-term observation, as TOF blocks signaling of multiple cytokine intracellularly.

The importance of MTX

MTX is the anchor drug for the treatment of RA. MTX is recommended for use as the first DMARD for the treatment of RA in patients who can tolerate it [2]. With MTX monotherapy, higher and rapidly escalated doses of MTX are effective and well tolerated, especially in Western populations [24]. Combination therapy with MTX and TNF-α inhibitors has been shown to be effective compared with MTX monotherapy [25–29]. However, the minimally effective dose of MTX used in combination with bDMARDs has not been determined. Recently, Burmester and colleagues reported the results of an RCT studying the minimal effective dose of MTX for combination therapy with ADA [30]. The authors randomly divided MTX- and bDMARDs-naïve early RA patients with DAS28-CRP ≥3.2, CRP ≥1.5 mg/dl, ≥1 bony erosion, and seropositivity into four groups receiving 2.5, 5,

10, or 25 mg MTX once weekly in a double-blinded manner (Fig. 3). All patients had received ADA 40 mg every 2 weeks in an open-label manner. Statistically significant increases in the percentage of patients achieving DAS-low disease activity (LDA; DAS28-CRP <3.2), DAS remission (DAS28-CRP <2.6), and simplified disease activity index remission (SDAI; ≤3.3) were seen with escalating doses of MTX in combination with ADA at 26 weeks (Fig. 4). Similar effects of increasing doses of MTX on the lack of progression rate of small joint destruction [modified total Sharp score (ΔmTSS) <0.5] and minimal clinically important differences in function [Health Assessment Questionnaire (HAQ) change ≤0.22 from baseline] were observed, although differences between groups were not significant (Fig. 4). However, there was no significant differences between 10 and 20 mg/week MTX doses on accelerating the efficacy of ADA. Compared with Western people, Asian subjects have lower body weight. Thus, in cases using combination therapy with bDMARDs and MTX, MTX 20 mg a week might be a higher dose than needed. More RCTs are required to determine the minimal effective dose of MTX for combination therapy with bDMARDs worldwide.

Adverse events associated with molecular-targeted therapies

Pneumonia, tuberculosis, *Pneumocystis jirovecii* pneumonia, interstitial pneumonitis, and viral infections such as hepatitis B, C, and herpes zoster (HZ) are severe adverse events observed during treatment with molecular-targeted agents. Patients on TNF-α inhibitors have a higher risk of such serious infections compared with patients on sDMARDs. There was no increased risk for malignancies in patients with bDMARDs therapy [31]. In terms of adverse events with tsDMARD, increased HZ rates were observed among patients treated with TOF, especially in an Asian population [32]. The best way to prevent infections during treatment with bDMARDs or tsDMARD is to screen patients for risk factors before starting therapy. Physicians should survey the past history of infections such as tuberculosis, hepatitis B and C by the interview, radiographic examination including computed tomography and laboratory tests including interferon-gamma release assay (IGRA) for *Mycobacterium tuberculosis* infection, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb). Two IGRAs are commercially available at the present time. They are the QuantiFERON® TB Gold In-Tube test (QFT-GIT) and SPOT®*TB* test (T-Spot). Furthermore, patients with RA are at increased risk of developing comorbid conditions and serious infections [33]; careful examination should be performed to detect abnormalities in cardiac function, renal function, liver function, the number of lymphocytes and white blood-cell count. Some of the important causes of serious adverse events during the treatments with bDMARDs or tsDMARD are preventable with such careful screenings and consultation with a pulmonologist or hepatologist if necessary [34]. Use of the HZ vaccination at the start of treatment with bDMARDs or tsDMARD is not recommended because the HZ vaccine is an active one.

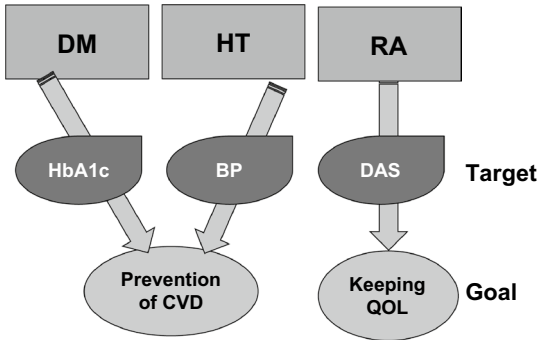

Fig. 5 Concept of treat-to-target strategy for diabetes mellitus (DM), hypertension (HT), and rheumatoid arthritis (RA). *BP* blood pressure, *DAS* disease activity score, *CVD* cardiovascular disease

Treat-to-target strategy (Fig. 5)

A treat-to-target (T2T) strategy [35] has been adopted in general practice in medicine. For example, the goal of treatment in diabetes mellitus (DM) or hypertension (HT) is the prevention of cardiovascular events. To reach the treatment goal in DM and HT, physicians start treatments after setting targets for HbA1c or blood pressure, respectively. Before the development of bDMARDs or tsDMARD, the use of a T2T strategy in the field of RA has been unrealistic. Currently, a T2T strategy is an effective approach using a combination of csDMARDs instead of bDMARDs, and use of bDMARDs is not essential for a T2T strategy [36]. In my opinion, the goal of RA treatment is to prevent a decline in QOL, and the current target to achieve this might be the DAS28 score. We are living in an era when it is easy to practice a T2T strategy by using bDMARDs or tsDMARD.

Limitations of molecular-targeted agents

RA is a heterogeneous chronic disease, and no therapeutic agent has been identified that is universally and persistently effective in all patients. This is also the case in bDMARDs or tsDMARD. It is difficult to predict clinical outcomes in RA in its natural course and during treatment with

bDMARDs or tsDMARD [37]. The use of molecular-targeted agents is associated with the adverse events reviewed above, as well as concerns regarding costs. After achieving good response with treatment with molecular-targeted medicines, it is uncertain that patients can maintain remission or low disease activity after stopping these drugs. The rates of patients maintaining targeted disease activity level after stopping bDMARDs in clinical trials driven by a T2T strategy were relatively low [38–40], and previous studies for the discontinuation of bDMARDs had several methodological limitations [41].

Conclusion

The development of bDMARDs and tsDMARD provided a wide range of treatment options for RA. We should consider the use of these agents using a T2T strategy after assessing the risks, benefits, and costs, as well as the impact of these agents on QOL. Long-term studies to confirm the results from short RCTs are required.

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Compliance with ethical standards

Conflict of interest The author has received research grants and consulting fees or other remuneration from and served on speakers' bureaus on behalf of AbbVie, Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Janssen, Mitsubishi Tanabe Pharma, MSD, Ono Pharmaceutical, Pfizer, Sanofi, Santen Pharmaceutical, Taisho Pharmaceutical, Takeda Pharmaceutical, Teijin Pharma, and UCB Pharma.

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