DMARDs. If the patients normalised MMP-3 and had low IL-6 levels, the retention rate reached 38%.[83] Further study will need to assess the impact of disease duration and DMARDs use on the duration of response after TCZ is discontinued. It is also unknown whether there will be a difference in the duration of sustained efficacy between early and established RA.

Evaluation of response and management of non-response

Response assessment should be done using composite measures of disease activity, such as DAS, DAS28, SDAI and CDAI. However, it should be borne in mind that APR are included in all of these except for the CDAI. Because the effect of IL-6 inhibition on CRP levels or ESR may be profound despite lack of clinical improvement, the actual response may be obscured (see above). Therefore measures that do not comprise an APR, such as the CDAI, are preferred (level 5, grade D). For the future, treatment goals based on modern imaging modalities that assess inflammatory activity, such as sonography or MRI, if shown to be associated with important outcomes, may be particularly relevant for patients using TCZ.

In line with respective recommendations,[13 14 59] disease activity assessment should be done initially monthly to every 3 months, aiming at a significant improvement within 3 months and attaining low disease activity (CDAI≤10, SDAI≤11, DAS28<3.2) or remission (using ACR-EULAR remission criteria[84]) within 6 months (level 5, grade D). Clinical trial data suggest that clinical efficacy is already seen within a few weeks[41 45 40] and, therefore, support the validity of the above recommendations for response expectations.

If a patient does not achieve low disease activity within 6 months at an adequate dose (or does not experience a significant improvement of disease activity within 3 months) another treatment option should be considered (level 5, grade D).

However, in the USA, where a starting dose of 4 mg/kg is licensed (and which may convey more immunogenicity and lower response rates as discussed above), a dose escalation may have to be considered much earlier if significant improvement is not attained. Specific data to guide such dose escalation are not well elaborated yet, since in clinical trials a dose increase from 4 to 8 mg was usually done only after 16 weeks and only in patients failing to achieve 20% reduction in tender and swollen joint counts, a quite minimalistic requirement given the baseline disease activity and length of time. Thus, in the case of dose escalation, judging response adequacy may be more appropriate after 3 and 6 months at the generally accepted therapeutic dose of 8 mg/kg.

Cost-effectiveness

Despite the relatively limited time since approval, some economic analyses on the use of TCZ have been published and, with all reservations regarding such analyses at a relatively early stage of use, revealed cost-effectiveness.[85 86] More data will be needed for full appreciation of the health economic aspects of TCZ use.

Contraindications, adverse effects and long-term exposure

TCZ has been studied in several international and Japanese trials, and most of these trials had long-term extension phases. The long-term safety in Japanese patients as well as in the international studies has been reported,[87 88] and also the SLR informing the present recommendations has focused partly on safety;[21] the reader is referred to these publications as well as the package insert.[35 55 87–89] A brief summary of adverse events as derived from the above-mentioned studies and the package insert is also provided in the online supplementary files, and some have been discussed above under "Screening before initiating TCZ". The items primarily addressed in the online supplement are hypersensitivity, infections including hepatitis, malignancies, changes of blood counts, lipids, gastrointestinal perforations, hepatic manifestations and cardiovascular risk.

Dose adaptation or discontinuation in case of adverse events and monitoring recommendations

While it is evident that in patients with infections, especially serious ones, TCZ therapy has to be interrupted or sometimes discontinued and therapy has to be withdrawn in the event of infusion reactions, there are also specific laboratory abnormalities that may require dose reductions or discontinuation. Thus if transaminase elevations in the range of 1–3×ULN persist, the dose should be reduced to 4 mg/kg or interrupted until normalisation; if transaminases increase to >3×ULN, therapy should be interrupted and can be resumed at lower dose when levels are <3×ULN, and resumed at 8 mg/kg after transaminase normalisation. For persistent (ie, seen at least twice) increases >3×ULN or for any elevation >5×ULN, TCZ should be permanently discontinued (level 5, grade D).

With respect to leukocytopenia, TCZ should be discontinued if neutrophil counts are <500/mm^3; at counts of 500–1000/mm^3, TCZ should be interrupted and resumed at 4 mg/kg once neutrophil counts increase to >1000/mm^3 (level 5, grade D).

Liver enzymes and bilirubin, complete blood count with differential and lipid levels should be assessed every 4 to 8 weeks for the first 6 months and every 3 months thereafter (level 5, grade D).

Patient perspectives

TCZ not only improves clinical signs and symptoms and joint damage, but also all pertinent patient reported outcomes, such as pain, physical function and quality of life; moreover, fatigue, an important symptom identified by patients with RA, is significantly improved with TCZ.[90] Patients should be fully informed by their rheumatologist about the benefits and risks of TCZ therapy. Treatment initiation as well as the treatment target should be based on a shared decision between the patient and physician and appropriately recorded (level 5, grade D).

Other indications and experiences

While the focus of the present statement is on adult RA, several other indications should be mentioned. TCZ is also licensed in Europe and Japan for systemic juvenile idiopathic arthritis (sJIA).[55] In Japan, TCZ is also approved for use in polyarticular JIA and Castleman's disease. These data are supported by respective publications[30 91 92] (level 1b to 2b, grade B). The specific indications and licensing may differ among other countries.

There are also a number of other diseases in which TCZ has been employed with or without success. According to several case reports, TCZ has been effective in patients with secondary amyloidosis, polymyalgia rheumatica, adult onset Still's disease, polymyositis, systemic sclerosis, large vessel vasculitis (such as giant cell arteritis), and it has also been used in Lupus with indications of some mild improvement.[92–101] However, none of these conditions are licensed indications and more information will have to be obtained from formal clinical trials. In part, these findings are in line with data on IL-6 inhibition in experimental models of these diseases.[102] In patients with Castleman's disease who frequently experience an interstitial pneumonitis, lung disease has improved upon TCZ therapy.[103 104] In contrast, TCZ has revealed negative results in case series and clinical trial of axial spondyloarthritis/

ankylosing spondylitis,[105–107] and this was also the case for a study on sarilumab, another IL-6R inhibitor.[108] Likewise, case reports in psoriatic arthritis showed no clinical effect of TCZ despite reduction in CRP,[109] although these were small studies in refractory patients. Nevertheless, the potential efficacy of antibodies to IL-6 rather than the IL-6R is currently unknown, and the potential efficacy of IL-6R blockade in patients with peripheral spondyloarthritis remains to be investigated.

Finally, TCZ has also been evaluated in a small pilot controlled study of Crohn's disease and showed limited efficacy (20% clinical remission without effects on endoscopic and histological changes) at doses of 8 mg/kg every other week.[110]

Research Agenda

The committee felt that many questions remained open and needed to be addressed in future research in both adult and paediatric populations. Some of these questions are presented herein; they focus on TCZ but would equally be pertinent for other compounds targeting the IL-6R or IL-6 and might be addressed in the course of planned clinical trials.

Dose of TCZ and concomitant therapies

- Can TCZ be withdrawn, its dose reduced or the interval of its administration expanded successfully in patients who have attained low disease activity or remission?
- In the USA: when is it ideal to increase the TCZ dose from 4 to 8 mg/kg and what are the indicators that should lead to this dose increase?
- Is TCZ monotherapy similarly effective as combination therapy with MTX in early and established RA?
- What is the effect of other IL-6i when used as monotherapy?

Efficacy and assessment aspects

- What is the most suitable remission or low disease activity target for TCZ, taking into account the specific effect on APR (CDAI and/or a newer imaging modality with assessment of synovitis activity?)
- Is IL-6 pathway inhibition efficacious in patients with active disease but normal CRP levels?
- What are predictors of response to IL-6-blockers?
- What are the effects of IL-6 inhibition on systemic osteoporosis?
- Is the use of IL-6 inhibitors economically sound?
- What is the comparative efficacy and safety profile of TCZ compared to other biological agents?

Safety in relation to other targeted therapies

- What are the efficacy and safety when IL-6 pathway inhibitors are given to patients previously treated with rituximab (with or without persistent B-cell depletion) or abatacept?
- How safe are TNFi, abatacept and rituximab after IL-6i therapy and vice versa?
- How safe are IL-6 inhibitors when combined with other sDMARDs besides MTX?
- Are IL-6 inhibitors safe when used with or immediately after Jak inhibitors, once these are licensed?
- Is there a need for a washout period after other biologicals have been employed or can IL-6 inhibition be applied when the next dose of the other biological is scheduled? And vice versa, is there a need for a washout period for TCZ before another biological can be used?

General safety aspects

- Is there a risk in patients with solid malignancies in the previous 5 years upon IL6 inhibition?
- Can patients with past/recent lymphoma or myeloma be safely treated with TCZ?
- How safe are IL-6 inhibitors in patients with diabetes?
- What is the net effect of IL-6-blockers on cardiovascular risk?
- What is the mechanism for the change in lipids seen with IL-6-blocking treatment?
- What is the involvement of IL-6 in defence against *Mycobacterium tuberculosis*? Is the risk of reactivation of latent tuberculosis truly increased among patients who receive TCZ or other IL-6 inhibitors?
- Is the response to vaccines impaired during IL-6-blocker therapy as it is during rituximab treatment?
- Is the risk of herpes zoster (shingles) increased with IL-6 inhibition?
- What are the predictors of anaphylactic reactions?
- How safe is the use of IL-6i in patients with hepatitis B or C, treated with or without antiviral agents?
- Does the use of isoniazid lead to significant increases in liver function tests in patients with IL-6 inhibitor mono- and combination therapy?
- What is the risk of GI perforations in patients treated with IL-6-blockers? Is there any specific GI perforation associated with these compounds, in the upper or lower gastrointestinal tract? Is it related or unrelated to concomitant use of other drugs?
- Is there a risk to exacerbate or trigger demyelinating disorders during treatment with IL-6 inhibitors?
- Are some forms of autoimmunity triggered upon the use of IL-6 inhibiting therapy?
- Is there a need to stop therapy with IL-6-blockers before fathering a child?
- What is the molecular effect of TCZ on target cells?

Other indications and aspects

- Larger trials should be performed for diseases like vasculitis (including giant cell vasculitis), polymyalgia rheumatica, poly- and dermatomyositis, systemic sclerosis, systemic lupus erythematosus, adult onset Still's disease, amyloidosis, and others.
- How should treatment with TCZ be approached in obese people?
- What is the efficacy and safety of using IL-6 inhibitors to treat extra-articular manifestations of RA, including interstitial lung disease and vasculitis?

CONCLUSION

In this consensus statement we provide recommendations for the use of IL-6 pathway inhibition in clinical practice. The data are primarily based on evidence assembled from clinical trials on TCZ, currently the only approved agent targeting this pathway, but also data of early phase clinical trials on other compounds that target both the IL-6 receptor and ligand have been considered. As far as available, these data confirm the efficacy and safety profile of IL-6 pathway blockade. Currently approved indications are adult rheumatoid and juvenile inflammatory arthritis. While other indications may follow with more available data, axial spondyloarthritis appears to be refractory to this therapy. The recommendations have been developed to provide guidance for rheumatologists and other physicians engaged in the treatment of inflammatory diseases as well as information for patients, payors and other stakeolders. They are summarised in the 'Points to Consider' (box 1). which provide only a synopsis of the discussions for purposes of general information. The details presented in the previous sections should be regarded as part and parcel of these points.

Additional data will be needed to fully understand the value of this treatment approach. Pertinent research question addressing

Box 1 Points to consider for the treatment of adult rheumatoid arthritis (RA) with tocilizumab (TCZ)*

Indication (level 1a, Grade A)

- RA with inadequate response to (or intolerance of) at least one synthetic disease modifying antirheumatic drug (sDMARDs) or tumour necrosis factor (TNF) inhibitor
  - Active RA (at least moderate disease activity according to a validated composite measure)

Contraindications (level 5, grade D)

- Allergy to TCZ
- Clinically relevant co-morbidities, particularly active infections

Pre-treatment screening (level 5, grade D)

- History and physical examination
  - Consider possible contraindications
  - Consider radiograph of the chest
  - Assess history of infections, diverticulitis and malignancies
- Routine laboratory testing, including lipid levels
- Testing for hepatitis B and hepatitis C viral infections
- Screening for tuberculosis
- Assess necessity of vaccination

Treatment dose and co-medication (level 1a, grade A)

- 8 mg/kg every 4 weeks as intravenous infusion, usually over 1 h
  - While the approved starting dose in the US is 4 mg/kg, this is not recommended by the task force.
  - A reduction from 8 to 4 mg/kg may be needed upon occurrence of certain adverse events.
- TCZ can be used in combination with methotrexate (MTX) (alternatively in combination with other sDMARDs) or as monotherapy, if MTX is inappropriate.
- Evaluation and definition of response (level 5, grade D)
- Apply validated composite indices to assess treatment response
  - Assess disease activity frequently especially during the first months after initiation of TCZ
  - Aim for remission (American College of Rheumatology-European League Against Rheumatism remission definition) or low disease activity state (LDA: disease activity score using 28 joint counts $\leq$ 3.2, simplified disease activity index $\leq$ 11, Clinical disease activity index $\leq$ 10)
  - A significant improvement should be achieved after 12 weeks and the treatment target should usually be reached after 24 weeks; insufficient response should normally lead to switching to an alternative therapy.
- Aim for improvement in function and quality of life
- Progression of structural changes should be prevented

Adverse events

- Infusion reactions (~7%)
  - Severe infusion (hypersensitivity) reactions may occur but are rare (0.3%); they are more frequent with the 4 mg/kg than the 8 mg/kg dose
- Serious infections occurred about twice as frequently with TCZ compared to placebo population
- Hepatic transaminase elevations
- Gastrointestinal perforations, primarily in patients with a history of diverticulitis
- Neutropenia and rarely thrombocytopenia
- Effects of uncertain relevance
  - Lipid increases (should be treated according to local guidelines)

*These points are a short abbreviation of the items discussed and presented in detail in the body of the text or in the online supplement. They should not be applied independently of the information provided there in more detail, but present only an overview of the general scope of the recommendations.

open issues on safety, efficacy and optimised use have been formulated. The expected advancements will allow for a more refined use of TCZ and other IL-6 inhibitors in the future. However, the already available information and the development of many additional biologicals targeting IL-6 or its receptor reveal the importance of this treatment option to improve the outcome in patients with RA, JIA and possibly other inflammatory diseases.

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Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions

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Notes

Discontinuation of biologics in patients with rheumatoid arthritis

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ABSTRACT

The use of early aggressive treatment combined with the availability of biological agents targeting pro-inflammatory cytokines such TNF and IL-6 has greatly advanced the treatment of rheumatoid arthritis (RA). Clinical remission is a realistic primary goal and its maintenance leads to stabilisation of structural deterioration and functional remission. With the achievement of sustained remission, discontinuation of biological agents has emerged as an important consideration, with subsequent reductions in medication-induced side effects and health costs.
Evidence from studies suggests that MTX-naïve, early RA patients can achieve sustained biologic-free remission with no functional or radiographic progression, after treatment with combination TNF inhibitors and MTX.
For patients with long-standing RA and who have previous inadequate responses to MTX, the evidence for sustained biologic-free remission is less convincing. The discontinuation of TNF-inhibitors after sustained remission has been shown to be possible in some long-standing RA patients with inadequate response to MTX, particularly in Japanese patients. However, high flare rates and adverse long-term outcomes have been documented in other studies.
For these patients a biologic dose-reduction regimen may be preferable.
The combination of early treatment with TNF inhibitors and MTX plus tight control of inflammation provide the best chance of a biologic-free remission or at least the possibility of "biologic treatment holidays".

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and premature mortality. However, the early use of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and the introduction of biological agents targeting TNF and other cytokines have revolutionised RA treatment (1-5). Clinical remission is perceived as an appropriate and realistic primary goal in many patients, and its maintenance – especially with biological agents – leads to structural and functional remission. Caution is required concerning decisions to discontinue synthetic DMARDs, as discontinuation results in twice as many flare-ups, difficulty in reintroducing remission, and a halt in damage prevention (6). However, similar studies are just becoming available for biological agents. The possibility of discontinuation of biological agents after achieving remission must be considered, because of both the potential long-term safety issues and the economic burden associated with their expense. Multiple studies have recently investigated whether remission can be sustained after a biological agent is discontinued, namely, "biologic-free remission." This article provides an overview of the literature regarding the discontinuation of TNF inhibitors and other biological agents in RA patients, after obtaining low disease activity or clinical remission.

Discontinuation of TNF inhibitors in patients with an inadequate response to MTX (MTX-IR)

The initial management of patients with newly diagnosed RA is aimed at controlling inflammation, maintaining function and preventing structural joint damage. For the majority of patients worldwide, MTX is now used as the first-line DMARD, with slight differences in regional and national algorithms for further DMARD and biological agents (7). The success of TNF-inhibitors in patients with inadequate responses to MTX is well documented (8, 9).

A Japanese group conducted a multi-centre prospective study, RRR (Remission induction by Remicade in RA patients), aimed at the possibility of

biologic-free remission in RA patients whose mean disease duration was 5.9 years (4, 5, 10, 11). This study included a total of 114 patients with RA who reached and maintained low disease activity (LDA; DAS28 <3.2) for more than 24 weeks with infliximab treatment, who then agreed to discontinue the treatment. Among the 102 evaluable patients who completed the study, 56 maintained LDA after one year and showed no progression in radiologic damage and functional disturbance, and 44 remained in clinical remission (DAS28 <2.6). The mean disease duration of the RRR-achieved group was 4.8±5.9 years, which made this study the first to prove that some patients with long disease duration may also aim for discontinuation. Yearly progression of total Sharp score was less than 0.5 points in 67% and HAQ-DI score was only 0.174 in patients who maintained LDA for one year after the discontinuation, indicating that infliximab could be discontinued for a year without radiographic or functional progression.

Another study from Japan, the HONOR (Humira discontinuation without functional and radiographic damage progressioN follOwing sustained Remission) study, aimed to assess sustained remission after discontinuation of adalimumab in patients with RA with MTX-IR (5, 12). Among 197 RA patients who initiated treatment with combination adalimumab and MTX (mean dose 9 mg/week), 75 achieved sustained remission for at least 24 weeks. Of the patients, 52 agreed to discontinue adalimumab. The mean disease duration and DAS28 score in 75 patients were 7.5 year and 5.1 at baseline, respectively.

Approximately 60% of patients sustained adalimumab-free remission at 6 months. A logistic regression analysis showed that the DAS28-ESR at baseline significantly predicted sustained adalimumab-free remission; a ROC analysis showed that the cut-off value of DAS28-ESR at discontinuation was 2.16. The HAQ-DI and yearly progression in total Sharp score also were unchanged after discontinuing adalimumab. Re-administration of adalimumab to the patients with flare was effective in achieving return to DAS28-4ESR <3.2 within 6 months by 90% of patients.

However, the above successful rates have not been observed in all patients. Saleem *et al.* assessed the effect of cessation of TNF inhibitor therapy (etanercept, adalimumab and infliximab) in patients with established previously severe RA (13). Twenty patients received combination therapy with TNF blocker and MTX after fulfilling the N.I.C.E prescribing guidelines for biologics therapy with median disease duration of 120 months (range 46–480 month). Patients in the delayed treatment group had failed at least two DMARDs (including MTX mean dose 15 mg/week) and 50% had also failed a previous TNF blocking drug (due to secondary non-response) (14). Only three patients were able to sustain remission after cessation of TNF blocking therapy.

Prior to stopping TNF blocking therapy, no significant differences were seen in DAS28 scores between patients who would subsequently sustain remission and those who would flare (median DAS28 1.96 *vs.* 1.67; p=0.84). However, patients who sustained remission after cessation of TNF blocking therapy tended to have lower HAQ (0 *vs.* 1; p=0.04) and RAQoL scores (1 *vs.* 4; p=0.17). No difference was seen in duration of remission before stopping therapy (12 *vs.* 12 months; p=0.68), but sustained remission also was associated with shorter total disease duration compared to flare (median 72 *vs.* 144 months; p=0.09). Of particular importance, despite reinstitution of TNF inhibitor therapy after flaring, DAS28 remission rates were lower than in patients who continued TNF inhibitor therapy (15).

Brocq *et al.* reported that patients with an average duration of RA of 11 years were withdrawn from TNF inhibitor therapy after being in DAS28-defined remission for at least six months. Seventy-five percent (15/20) of patients flared 12 months after the withdrawal of TNF inhibitor therapy (16).

Similar results were observed in the CERTAIN study, which aimed to evaluate the maintenance of remission following withdrawal of certolizumab pegol in patients with low-to-moderately active, long-standing RA despite DMARDs (17). Following 24 weeks double-blinded treatment with certolizumab pegol (n=96) or control (MTX and steroid) (n=98), patients in remission at both weeks 20 and 24 stopped the randomised therapy but remained on conventional DMARD. Among patients randomised to certolizumab pegol, 18.8% had CDAI remission at both weeks 20 and 24 and stopped the therapy, compared to 6.1% of patients randomised to control treatment. After discontinuation, CDAI remission or LDA was retained up to week 52 in 3/17 or 7/17, respectively, in patients with prior certolizumab pegol *vs.* 2/6 in patients with prior control treatment. SDAI remission was observed in 4/17 prior certolizumab pegol and DAS28 (ESR) remission in 4/17 prior certolizumab pegol. Median time to loss of CDAI remission was 42.5 days. These results indicate that most patients with long-standing RA were unable to maintain remission after discontinuing certolizumab pegol.

There are differences between types of patients studied in the above trials that may account for the different clinical outcomes. The patients from the Japanese trials (4, 5, 10-12) were begun on TNF-inhibitor therapy after failing MTX, defined as DAS28 >3.2, whereas the patients in the Leeds cohorts (13) fulfilled much stricter criteria before they were considered MTX inadequate responders and TNF inhibitor therapy was commenced. The latter group would therefore represent a more severe, treatment-resistant group of patients with longer disease duration. The mean doses of MTX in the Japanese studies were 7.7±2.3 mg/week in RRR and 8.9±2.7 mg/week in HONOR, which, as is generally the case in Japan, were considerably lower than in other studies from elsewhere. These differences in study protocol, along with the potential impact of genetic differences of the patients, must be considered.

Dose reduction of TNF inhibitors in patients with an inadequate response to MTX (MTX-IR)

The PRESERVE trial was undertaken to determine whether LDA could be sus-

tained with reduced doses or withdrawal of etanercept in patients with moderately active RA despite MTX (18). After treatment with 50 mg etanercept plus MTX for 36 weeks, 604 patients were randomised to 3 groups in equal numbers: 50 mg etanercept plus MTX; 25 mg etanercept plus MTX; or placebo plus MTX. At week 88, 52 weeks after randomisation, LDA had been maintained in 84 (42.6%) of 197 patients randomised to placebo plus MTX, *versus* 166 (82.6%) of 201 patients who had received at least one dose of 50 mg etanercept and 159 (79.1%) of 201 given 25 mg etanercept. From these results, conventional or reduced doses of etanercept with MTX in patients with moderately active RA more effectively maintain LDA than does MTX alone after withdrawal of etanercept, but LDA was sustained with MTX alone in 42.6% of patients after discontinuing etanercept.

Discontinuation of Abatacept in patients with an inadequate response to MTX (MTX-IR)

The ORION (Orencia Remission Induction and Outcome Navigation) study group assessed abatacept-free remission in 51 RA patients with a DAS28 <2.3 while taking abatacept, in whom the agent was then discontinued or continued. At week 52, 41.2% of the discontinuation group and 64.6% of the continuation group maintained low disease activity. The patients in the discontinuation group (who were given the option of stopping therapy) had a lower mean disease duration compared to those who chose to continue therapy. Furthermore, 14.3% of patients who discontinued abatacept sustained rapid radiographic deterioration; it is unclear from the abstract whether these patients continued a traditional DMARD such as MTX (19).

Discontinuation of Tocilizumab in patients with an inadequate response to MTX (MTX-IR)

Mexican patients in DAS28 remission discontinued tocilizumab and continued MTX therapy (20). Forty patients were recruited, mean disease duration 14 years, and 44% maintained remission at 12 month follow-up. These patients all had received tocilizumab as part of different trial protocols, *i.e.* some patients received tocilizumab after failing TNF inhibitors, some after DMARD failures, and others were MTX-naïve.

The DREAM [Drug-free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy] study investigated remission and LDA after cessation of tocilizumab monotherapy in patients with previous inadequate response to MTX (21). At the time of stopping tocilizumab, patients had received a mean 4 years of treatment. The rate of LDA without concomitant use of synthetic DMARDs was 35.1% at 24 weeks and 13.4% at 52 weeks according to the Kaplan-Meier estimate. DAS28 remission and 2011 ACR/EULAR remission criteria (Boolean approach) were maintained in 17 patients (9.1%) and 14 patients (7.5%), respectively, at 52 weeks. In patients who flared after cessation of tocilizumab, 88.5% regained remission after restarting tocilizumab and therapy was well tolerated.

The rate of drug-free remission after tocilizumab monotherapy seems comparable to rates of sustained remission after stopping TNF inhibitor therapy and continuing MTX, but may be improved if DMARDs are continued. However, the heterogeneous nature of the prior therapies in clinical trials prevents direct comparison.

Discontinuation of TNF inhibitors in MTX-naïve RA patients

The central dogma of "treat-to-target" is that abrogation of inflammation from the onset of the disease should prevent joint damage and preserve physical function, which leads to overall improved quality of life and survival. Thus, the management of RA should shift towards earlier and more intensive treatment strategies. Studies using biologic agents targeting TNF, IL-6 and T cells have proven that intensive initial biologic therapy in early RA patients who have never been treated with MTX results in the improvement of clinical, structural and physiological outcomes over both the short and long terms. Several studies, including TNF20, BeSt, OPTIMA, HIT HARD, IDEA and PRIZE have recently been undertaken to investigate whether remission can be sustained even if a TNF-inhibitor is discontinued after controlling disease activity in early RA patients

A pivotal study concerned with biologic-free remission was performed by Quinn *et al.* (22, 23). Patients with early, active RA were recruited into a 12-month randomised placebo-controlled double-blind trial of infliximab with MTX, with the aim of inducing remission. The primary outcome was synovitis as measured by MRI. At 12 months, all MRI scores were significantly better, with no new erosions in the infliximab+MTX group. The patients in the active treatment arm also achieved higher ACR 50 and 70 responses. Importantly, one year after stopping induction therapy, response was sustained in 70% of patients who had received infliximab+MTX, with a median DAS28 of 2.05.

Saleem *et al.* published a sustained remission rate of 60% after discontinuation of TNF inhibitor therapy in MTX-naïve patients in DAS28 remission after one year of combination therapy. Evidence was found that sustained TNF-inhibitor-free remission was associated with shorter symptom duration prior to receiving therapy (median 5.5 *vs.* 9.0 months, p=0.008) (13).

In the Netherlands, the Behandel-Strategieën (BeSt) study was conducted to compare four treatment strategies and to observe clinical and radiological outcomes in patients with early RA (24-28). Patients with disease duration less than 2 years after onset were enrolled and the mean disease duration was 0.8 years. This pragmatic non-blinded study design recruited 508 patients with high disease activity into four treatment arms. Patients were evaluated by DAS44 every three months. If DAS44 >2.4 (moderate to high disease activity), change or addition of medications is required; if DAS44 ≤2.4 (remission or LDA), current medication is continued; and if DAS44 ≤2.4 continued over 6 months, decrease and/or discontinue concomitant medications including infliximab (see Allaart *et al.* p. S14-S18).

Ninety (75%) patients of 120 in the fourth group who started treatment with infliximab achieved DAS44 ≤2.4; infliximab was withdrawn in 77 patients because DAS44 ≤2.4 was maintained for 6 months. LDA was maintained and progress of joint damage was inhibited in 67 of 77 (87%) patients who were treated with MTX monotherapy for 2 years after infliximab withdrawal. Furthermore, 5 years after receiving infliximab and MTX as initial treatment for RA, 58% of 120 patients discontinued infliximab and 19% of patients have discontinued all DMARD and remained in clinical remission, with minimal joint damage progression. In addition, the total cost of work loss and medical expenses could be suppressed to less than half in the fourth group which was treated with MTX and infliximab initially, compared to other groups whose initial therapy involved only DMARD.

The withdrawal of adalimumab in early RA patients (with a mean RA duration of 3.9 months) was also assessed in a randomised, placebo-controlled, double-blind trial OPTIMA (Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab) (29, 30). The OPTIMA study showed a significant advantage of initial treatment with adalimumab+MTX *vs.* placebo+MTX to achieve improved disease activity, structural changes, patient-reported outcomes and work productivity outcomes in patients with MTX-naïve RA. The requirement for randomisation to discontinuation was achievement of LDA at both 22 and 26 weeks.

Of the 466 RA patients treated with adalimumab+MTX for 24 weeks, 207 (44%) achieved the stable LDA and were re-randomised to placebo+MTX or adalimumab+MTX. At week 78, 86% treated with adalimumab+MTX and 66% treated placebo+MTX maintained DAS28 remission. SDAI-remission and ΔmTSS remission were comparable for both groups. More patients with continuous adalimumab maintained LDA (91%) than did patients in the adalimumab-free group (81%). In the combined group (consisting of placebo+MTX or adalimumab+MTX), patients with sustained LDA between weeks 26 and 78 maintained or improved work productivity, whilst those who did not sustain LDA worsened with respect to these outcomes. However, continued use of adalimumab+MTX yields better benefits with respect to work productivity than discontinuation of adalimumab for patients who achieve LDA following 26 weeks of adalimumab+MTX.

The withdrawal of adalimumab in early RA patients with mean RA duration of 1.7 months was also assessed in a German study, HIT HARD (High Induction THerapy with Anti-Rheumatic Drugs) (31). During the first 24 weeks, 172 patients were treated with adalimumab+MTX or placebo+MTX. After week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase, 47.0% of patients treated with adalimumab+MTX achieved DAS28 remission, and at week 48, 43.8% were still in remission after 24 weeks of adalimumab-free treatment.

Other studies have been designed to determine rates of TNF-inhibitor-free remission in MTX-naïve patients with early RA. The IDEA (Infliximab as induction therapy in Early rheumatoid Arthritis) study was a randomised controlled trial in DMARD-naïve early RA to compare the efficacy of MTX plus a TNF inhibitor *versus* MTX combined with IV steroid therapy as remission-induction, followed by a treat-to-target approach. A treat-to-target approach was used with treatment escalation if DAS44 >2.4. In the IFX group, IFX was discontinued for sustained remission (DAS44 <1.6 for 6 months). Of the IFX group, 24.5% (14/55) had stopped IFX due to sustained (>6 months) remission and 78.6% (11/14) of them maintained remission (32).

The PRIZE study aimed to determine the effectiveness of etanercept (ETAN) and MTX therapy in MTX-naïve early RA patients who had moderately active disease (33). DAS28 remission was achieved by 70% of patients, and these patients were subsequently randomised to a double-blind 39-week period of reduced-dose etanercept (25 mg) plus MTX, or MTX plus placebo sc, or placebo PO and placebo sc. Sustained remission was observed in 63.5% of patients with ETAN25/MTX, 38.5% with MTX (those who discontinued etanercept) and 23% with placebo (those who discontinued etanercept and MTX). There was no significant radiographic progression in any treatment group (34).

Discontinuation of TNF inhibitors in MTX naïve very early RA patients

With accumulating evidence in support of early treatment with combination TNF inhibitor/biological agent and MTX therapy, identification of patients with very early disease is paramount, and the question arises to whether treatment in the at the onset of IA can prevent or delay the development of RA. The results so far are inconclusive, with evidence that abatacept may reduce the progression to RA (35), but a 6-month course of infliximab monotherapy was unsuccessful (36). The EMPIRE (Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis) trial aimed to investigate clinical, radiographic and functional outcomes, comparing the efficacy of combination therapy with MTX+ETAN *versus* MTX monotherapy, in subjects with DMARD-naïve very early inflammatory arthritis with the minimum of one synovitic joint. One hundred and ten DMARD-naïve patients were recruited into this 78-week multicentre randomised controlled trial and were randomised 1:1 to receive MTX+ETAN or MTX+placebo (PBO) for 52 weeks. Injections were stopped in all patients at week 52; in those with no tender or swollen joints (NTSJ) for >26 weeks, injections were stopped early. If patients had NTSJ >12 weeks after stopping the injections, MTX was weaned. Initial results suggest that of the patients in the MTX+ETN group, 41.9% remained in DAS28 remission from week 52 to week 78 and 57.7% remained in LDA according to DAS28 (37).

Tight control and treatment holiday

Although there are limited studies, "a biologic treatment holiday" not only in patients with early RA but also some select group of patients with long-established RA is possible. Infliximab

and adalimumab seem to have a better potential for their discontinuation than certolizumab pegol or etanercept as shown in the studies of TNF20, BeSt, HIT HARD, OPTIMA and PRIZE in early RA, and RRR and HONOR in established RA (10-37). However, there is evidence that etanercept dose reduction can maintain sustained remission (18, 34). A direct comparison of the studies presented here is not possible due to differences in study design, inclusion criteria and outcomes, *i.e.* remission *versus* LDA, and diverse remission criteria. Further work is also required to determine the effect of cessation of other biological drugs such as tocilizumab and abatacept, and the roles their different mechanisms of action may play.

There are pharmacologic differences between the available TNF inhibitor drugs. A monoclonal antibody to the TNF, such as infliximab or adalimumab, blocks the biological functions of TNF via binding to not only soluble TNF but also transmembrane TNF, whose binding induces complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and outside-to-in signaling, which would produce apoptosis to pathogenetic cells bearing membrane-bound TNF (38-40). Therefore, biologic-free remission might be highly expected in infliximab and adalimumab with the mechanisms of action to be able to eradicate the root cause of joint inflammation.

After achieving LDA or remission the goal of therapy is to maintain a clinical, functional and structural remission state. For some patients this is possible even after the cessation of the biological drug. However, there are no guidelines or reliable predictive markers that allow the identification of such patients. Questions arise as to the optimal method of defining remission and whether there is a need for more objective assessments of remission that would include imaging (MRI, US) and immunological markers of inflammation (T cells, T regulatory cells).

Guidelines exist for the initiation of biological drugs exist, but not for their discontinuation. EULAR 2012 guidelines suggest that after remission has been sustained for at least 12 months, gradual dose reduction should be attempted. van den Broek *et al.* recently published three recommendations for discontinuation of biological drugs (41):

1. If patients have low disease activity or been in remission for at least 6 months, consider trying it.
2. Once biologics are discontinued, keep monitoring disease activity, functional ability and radiological damage progression.
3. Restart treatment as soon as it appears that the disease is relapsing.

Conclusion

For patients with established disease (MTX-IR), the evidence suggests that for some patients, especially in Japan, successful biological drug cessation is possible but dose reduction is more consistently successful. For MTX-naïve patients, treatment with combination TNF inhibitor therapy and MTX results in high remission rates and also a 60–70% chance of sustaining remission after cessation of TNF inhibitor therapy. Such an early intensive approach to patients with new-onset RA, with limited biologic use, would have the potential of reducing drug-induced adverse effects and reducing long-term health costs – although the risks of worsening clinical, functional and radiographic outcomes must be considered, with measures in place for careful monitoring of status, prompt re-assessment and re-introduction of therapy. Further data are eagerly awaited that will provide evidence for the ideal remission induction regime and predictors for successful cessation of therapy. Such data could provide objective markers of disease to enable an individualised approach to the management of patients in remission.

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Is It Possible to Withdraw Biologics From Therapy in Rheumatoid Arthritis?

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ABSTRACT

Background: Biologic agents targeting tumor necrosis factor (TNF) have revolutionized the treatment of rheumatoid arthritis (RA). Clinical remission is perceived as a realistic primary goal, and its maintenance leads to structural and functional remission.

Objective: This study reviews whether discontinuation of biologic agents is possible after sustained remission and discusses its significance from the risk/benefit point of view (including safety and health economic considerations).

Methods: Using a strategic PubMed search, 45 original research articles regarding discontinuation of biologic agents were identified; 7 were selected that had an obvious focus on discontinuation of biologic agents. These articles included the TNF20, BeSt (Behandel Strategieen), and RRR (Remission Induction by Remicade in RA) studies. However, because of the limitations of the original search, we also review here some articles that did not focus mainly on discontinuation of biologic agents but that presented data regarding biologic-free control. These studies included OPTIMA (Optimal Protocol for Treatment Initiation With MTX and Adalimumab), PRESERVE, and CERTAIN, as well as some recent findings in the HONOR (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission) study from our department.

Results: In BeSt and OPTIMA, clinical remission was sustained without functional progression by discontinuing TNF inhibitors, after reducing disease activity by using TNF inhibitors and methotrexate (MTX), in patients with early RA and who were MTX naive. In some studies (including RRR and HONOR), the discontinuation of TNF inhibitors after sustained remission was possible in some patients with long-standing RA who had an inadequate response to MTX. When disease activity flared up after treatment discontinuation, re-treatment with infliximab or adalimumab was highly effective and safe in the majority of patients. It is also clear that tight control with TNF inhibitors and MTX seems to be a prerequisite for having a better chance of biologic-free remission.

Conclusions: Intensive treatment with TNF inhibitors may change the disease process of RA and potentially offers the possibility of a "treatment holiday" from biologic agents. (*Clin Ther.* 2013;35:2028–2035)

Key words: biologic, discontinuation, remission, rheumatoid arthritis, treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction that causes significant morbidity and mortality. To prevent joint damage, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) should often be started after patients are diagnosed. However, the use of MTX monotherapy often fails to control disease activity and to prevent structural damage, and more effective treatment strategies are thus needed. TNF plays a pivotal role in the pathologic processes of RA through the accumulation of inflammatory cells and the self-perpetuation of inflammation, which leads to joint destruction. The combination of MTX and biologic agents targeting tumor necrosis factor (TNF) has revolutionized the treatment of RA, producing significant improvements in clinical, radiographic, and functional outcomes that were not previously observe. The combination has produced the emerging outcome and upcoming end

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point for the treatment as the followings.[1–5] Clinical remission is perceived as an appropriate and realistic primary goal in many patients, and its maintenance leads to structural and functional remission.

The possibility of discontinuation of biologic agent treatment after achievement of remission or low disease activity must be considered because of the long-term safety issues found by inhibiting a particular cytokine and the economic burden associated with expensive biological products. The decision to discontinue synthetic DMARDs should be made with caution; such discontinuation results in twice as many flare-ups, difficulties in reintroducing remission, and a halt in damage.[6] However, similar studies are not available for the biologic agents it remains unclear whether treatment strategies with biologics targeting induction and/or maintenance of clinical remission can potentially lead to subsequent discontinuation of the TNF inhibitors. The goal of the present article was to determine if discontinuation of biologic agents targeting TNF is possible in RA patients, after obtaining low disease activity or clinical remission during certain periods of use with TNF inhibitors. The content is based on results of a systemic literature review as well as new information.

METHODS

A search of PubMed was conducted by using a search strategy that combined terms for *rheumatoid arthritis, biological agent*, and *discontinuation, discontinuing*, or *cessation*. The systematic literature search strategy was as follows: #1, arthritis, rheumatoid [MeSH]; #2, biological agents OR biologics OR TNF inhibitor OR infliximab OR etanercet OR golimumab OR abatacept OR tocilizumab OR certolizumab pegol; #3, clinical trial [Filter]; #4, English [Filter]; #5, discontinuation OR discontinuing OR cessation; #6, review [Filter]; #7, juvenile idiopathic arthritis; and #8, #1 AND #2 AND #3 AND #4 AND #5 NOT #6 NOT #7.

The titles and abstracts of the citations were screened, and relevant articles were retrieved. The following selection criteria were used: (1) clinical trials of biologic agents in patients with RA, followed by discontinuation of the biologic agents due to preferable effectiveness but not to adverse events or to insufficient efficacy; (2) patients with RA aged >18 years; and (3) data available on 1 or more of the following prespecified outcomes: ratio of remission or low disease activity after at least 12 weeks of discontinuation or ratio of re-administration of the biologic agents.

Forty-five original research articles were identified from the PubMed search; 7 articles were selected as candidate studies, and 38 articles were excluded from our analysis. All of the included and excluded articles were published since 1998. The reasons for exclusion were categorized into 3 groups: (1) no description of discontinuing biologic agents; (2) reasons for discontinuing biologic agents were not specified; and (3) no description of discontinuing biologic agents due to preferable effectiveness. Characteristics of the candidate studies are summarized in the Table.[7–13]

The majority of the excluded articles focused on the efficacy and safety of certain biologic or synthetic DMARDs but not on discontinuation after attaining preferable disease control. The 7 included articles focused on discontinuation of biologic agents. However, those studies were published from a limited number of nations or institutes, and 4 were subanalyses of the BeSt (Behandel Strategieen) study and 2 were subanalyses of the RRR (Remission Induction by Remicade in RA) study. In addition, published evidence regarding biologic-free disease control is limited in cases of infliximab. We therefore reviewed some articles that did not mainly focus on discontinuation of biologic agents but that included data regarding biologic-free control, including the OPTIMA (Optimal Protocol for Treatment Initiation With MTX and Adalimumab), PRESERVE, and CERTAIN studies. We also included recent findings from the HONOR (Humira Discontinuation Without Functional and Radiographic Damage Progression Following Sustained Remission) study from our department.

RESULTS

Can We Discontinue Infliximab?

Infliximab is an anti-TNF chimeric monoclonal antibody that was approved for the treatment of RA in 1999 in the United States and the European Union. The study regarding biologic-free treatment in RA patients was first reported by a British group as a TNF20 study.[9,14] Patients with early RA who had <12 months of symptoms were treated with a combination of infliximab and MTX. Patients who initiated treatment with infliximab and MTX achieved higher American College of Rheumatology 50% and 70% improvement

Table. Summary of the candidate studies for discontinuation of biologic agents in patients with rheumatoid arthritis.

Author	Study	Nation	Biologic	DMARD	Criteria	Observation Period	No. of Discontinuations	Failed or Restarted	Effect of Restarting Biologic
van den Broek et al[7]	BeSt	NL	IFX	MTX	DAS $\leq$2.4 at 6 mo	7.2 y (median)	104 (52%): all 77: initial IFX + MTX	48% restart, 17 mo (median)	84% DAS $\leq$2.4
Klarenbeek et al[8]	BeSt	NL	IFX	MTX	DAS $\leq$1.6 at $\geq$6 mo	5 y	115/508 (23%): drug-free	53/115 (46%) restart, 23 mo (median)	39/53 (74%) DAS $\leq$1.6
Bejarano et al[9]	TNF20	UK	IFX	MTX	No criteria (randomized)	8 y	10 discontinued (1 died,) 4/9 REM, 1/4 drug free	5/9 (56%) failed	NS
Tanaka et al[10]	RRR	JPN	IFX	MTX	DAS28 $\leq$3.2 at >24 wk	1 y	114 discontinued, 102 evaluated at 1 y	46/102 (45%) failed	NS
Nawata et al[11]	CS	JPN	IFX	MTX	DAS28 <2.6 at $\geq$24 wk	NS	5% (9/172)	No. and %: NS, 14 mo (mean)	NS
van der Kooij et al[12]	BeSt	NL	IFX	MTX	DAS $\leq$ 2.4 at $\geq$6 mo	2 y	56% (66/117) initial IFX 29% (19/67) delayed IFX	NS	NS
van der Bijl et al[13]	BeSt	NL	IFX	MTX	DAS $\leq$2.4 $\geq$6 mo	2 y	56% (67/120) median 9.9 mo	15% (10/67) restart, median 3.7 mo	NS

BeSt = Behandel Strategieen; CS = case series; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug(s); IFX = infliximab; JPN = Japan; MTX = methotrexate; NL = the Netherlands; REM = remission; RRR = Remission Induction by Remicade in RA; UK = United Kingdom.

responses than those initiating therapy with MTX and placebo. One year after stopping induction therapy, response was sustained in 70% of patients who received infliximab and MTX. A significant reduction in magnetic resonance imaging evidence of synovitis and erosions at 1 year was also observed.

In the Netherlands, the BeSt study was conducted to compare 4 treatment strategies in patients with early RA.[7,8,12,13,15] Patients with disease duration <2 years after onset and a disease duration of 0.8 year were enrolled. A total of 508 patients with high disease activity estimated by using the Disease Activity Score in 44 joints (DAS44) were assigned to 4 groups and were evaluated by using the DAS44 every 3 months. DAS44 is a clinical assessment tool to integrate measures of disease activity which consists of swollen joint count and tender joint count of 44 joints, patient-evaluated global disease activity and CRP or ESR. Ninety (75%) of 120 patients in the fourth group who started treatment with infliximab achieved low disease activity, as shown by a DAS44 score ≤2.4; in 77 patients, infliximab was withdrawn because a DAS44 score ≤2.4 was maintained for 6 months. Low disease activity was maintained and progress of joint damage was inhibited in 67 patients who were treated with MTX monotherapy for 2 years after infliximab withdrawal. Furthermore, 5 years after receiving infliximab and MTX as initial treatment for RA, 58% of 120 patients had discontinued infliximab and 19% of patients had discontinued all DMARDs and remained in clinical remission or low disease activity, with minimal joint damage progression.

We initially conducted a multicenter prospective study (RRR) focused on the possibility of biologic-free remission in RA patients whose mean disease duration was 5.9 years.[4,5,10,11] This study included 114 patients with RA who reached and maintained low disease activity for >24 weeks with infliximab treatment. Among the 102 evaluable patients who completed the study, 56 maintained low disease activity after 1 year and showed no progression in radiologic damage and functional disturbance. The mean disease duration of the RRR achieved group was 4.8 (5.9) years, which made this study the first to prove patients with longer disease duration. It is noteworthy that re-treatment with infliximab in 32 patients was effective, and the majority of patients reached low disease activity (DAS28 scores <3.2) within 24 weeks. Minimal adverse reactions at infusion of the agent were seen in 5 patients only at the first or second infusion.

Can We Discontinue Etanercept?

Etanercept is a fusion protein of the TNF receptor and Fc of immunoglobulin G approved for RA treatment in 1998 in the United States and the European Union. Both the efficacy and safety of etanercept are well established. The PRESERVE trial was undertaken to determine if low disease activity could be sustained with reduced doses or withdrawal of etanercept in patients with moderately active RA despite MTX therapy.[16] After treatment with 50 mg of etanercept plus MTX for 36 weeks, 604 patients were randomized equally to receive 50-mg etanercept plus MTX, 25-mg etanercept plus MTX, or placebo plus MTX. Fifty-two weeks after randomization, 50 or 25 mg of etanercept with MTX in patients with moderately active RA more effectively maintained low disease activity (82.6% and 79.1%, respectively) than MTX alone after withdrawal of etanercept; low disease activity was sustained with MTX alone in 42.6% of patients after discontinuing etanercept.

Can We Discontinue Adalimumab?

Adalimumab is a fully human anti-TNF monoclonal antibody approved for RA treatment in 2003 in the United States and the European Union. The OPTIMA study reported a significant advantage with initial treatment with adalimumab plus MTX versus placebo plus MTX for achieving improved disease activity and structural changes in patients with MTX-naive RA and a mean RA duration of 3.9 months.[17,18] Of the 466 RA patients treated with adalimumab and MTX for 24 weeks, 207 (44%) achieved a stable DAS28 score (low disease activity) and were re-randomized to receive placebo or adalimumab with MTX. At week 78, more patients with continuous adalimumab treatment maintained low disease activity (91%) or remission (86%) than did patients in the adalimumab-free treatment group (81%) or remission (66%). Thus, withdrawal of adalimumab was possible in 66% to 81% of patients with early RA after achieving low disease activity. However, continued use of adalimumab and MTX yields better benefits with respect to work productivity than discontinuation of adalimumab.

The withdrawal of adalimumab in patients with early RA (mean RA duration, 1.7 months) was also assessed in a German study (designated HIT HARD).[19] During the first 24 weeks, 172 patients were treated with adalimumab or placebo with MTX;

after week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase, 47% of patients treated with MTX and adalimumab achieved DAS28/remission; at week 48, 44% of these patients were still in remission by 24 weeks of adalimumab-free treatment.

Our group has performed a study (HONOR) similar to RRR by using adalimumab to investigate whether a sustained remission is preserved after discontinuation of adalimumab in patients with RA and an inadequate response to MTX.[5,20,21] Among 197 patients with RA who initiated treatment with a combination of adalimumab and concomitant MTX, 75 acquired sustained remission for at least 24 weeks. Fifty-one of these patients agreed to discontinue adalimumab, but 1 was lost to follow-up. The mean disease duration and DAS28 score in 75 patients was 7.1 years and 5.1 at baseline, respectively. Twenty-nine (58.0%) of the 50 patients achieved adalimumab-free remission at the primary end point of 6 months after discontinuation. However, 21 patients (42%) failed to maintain adalimumab-free remission for 6 months. Twelve of those patients (24%) experienced disease exacerbation, defined as DAS28 score using an erythrocyte sedimentation rate (ESR) >3.2 within a 6-month adalimumab-free period. Nine patients agreed to increase the MTX dosage and/or re-start adalimumab at the exacerbation. Among 12 patients with disease exacerbation, 5 of 6 patients re-treated with adalimumab returned to at least low disease activity within 6 months. Restarting adalimumab due to relapse was not associated with any harmful effects. These results, taken together with the results of the RRR study, suggest that restarting TNF inhibitors seems to be effective and safe even after a treatment holiday.

Can We Discontinue Certolizumab Pegol?

Certolizumab pegol is a recombinant, humanized antibody Fab' fragment, with specificity for human TNF, conjugated to 40 kDa of polyethylene glycol. It was approved for the treatment of RA in 2009 in the United States and the European Union. The CERTAIN study was undertaken to evaluate the maintenance of remission after withdrawal of certolizumab pegol in patients with low to moderately active RA despite DMARD therapy.[22] After 24 weeks of double-blind treatment with certolizumab pegol or placebo, 18.8% of patients treated with certolizumab pegol experienced remission (based on the clinical disease activity index [CDAI]) at both weeks 20 and 24; they discontinued the randomized therapy but remained on conventional DMARD treatment. After discontinuation, CDAI-categorized remission or low disease activity was retained up to week 52 in 3 and 7 patients, respectively, of the 17 patients who previously received certolizumab pegol treatment. Median time to loss of CDAI-categorized remission was 42.5 days. These results indicate that most patients with long-standing RA were unable to maintain remission after discontinuing certolizumab pegol.

What Is Relevant to the Discontinuation of Biologic Agents?

Recent studies indicate that some patients could discontinue TNF inhibitors without clinical flare and functional impairment after reduction of disease activity to low levels or remission by TNF inhibitors such as infliximab and adalimumab in combination with MTX. Although there are limited studies, a treatment holiday of TNF inhibitors seems possible in patients with not only early RA but also long-established RA. However, among multiple TNF inhibitors, infliximab and adalimumab seem to have the better potential for discontinuation than certolizumab pegol or etanercept, as shown in the studies of TNF20, BeSt, HIT-HARD, and OPTIMA in early RA, and RRR, HONOR, PRESERVE, and CERTAIN in established RA.[7–22] A monoclonal antibody against TNF such as infliximab and adalimumab blocks the biologic functions of TNF via bindings to not only soluble TNF but also transmembrane TNF, whose binding induces complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and outside-to-inside signaling, which would induce apoptosis to their pathogenic cells bearing membrane-bound TNF.[23–25]

However, not all patients with remission maintained that status even after discontinuation of adalimumab and infliximab. In the RRR study, 55% of patients sustained infliximab-free low disease activity for 1 year.[5,10] According to multivariate analysis, DAS28 scores at RRR study entry had the most marked correlation with the maintenance of low disease activity for 1 year after the discontinuation. By logistic regression and a receiver-operating characteristic curve analysis, the cutoff point for achieving RRR outcome, keep DAS28 <3.2 without flare, at the

time of patient enrollment was a DAS28 score of 2.225. In fact, 71.4% of patients whose DAS28 score at study entry was <2.225 maintained low disease activity for 1 year, whereas only 32.6% of patients whose DAS28 score at RRR entry was 2.225 to 3.2 maintained low disease activity. This finding indicates that "deep remission" was required to maintain low disease activity for 1 year after discontinuation of infliximab.

In the HONOR study, 58% of patients sustained adalimumab-free remission at 6 months.[5,20,21] A logistic regression analysis found that a lower DAS28-ESR score at discontinuation was the most significant predictive factor for adalimumab-free remission for 6 months, and a receiver-operating characteristic curve analysis found that the cutoff value of DAS28-ESR at discontinuation was 2.16. The percentage of patients who retained sustained remission at 6 months was 78% in the patient group with DAS28-ESR scores ≤2.16 at study entry and 22% in the patient group with scores of 2.6> DAS28-ESR >2.16. These results indicate that deep remission through tight control of disease activity at the discontinuation of biologic agents seems to be a prerequisite for the successful treatment holiday; these findings are analogous to those from RRR.

Thus, we have to realize that "intensive treatment" with TNF inhibitors is possible for efficiently bringing about a treatment holiday, as deep remission was shown to be a major factor affecting the success of the discontinuation of TNF inhibitors in 2 Japanese studies.[10,20,21] Furthermore, in our institution, among 577 patients who were treated with infliximab, 88 patients became free of biologic agents. By multivariate analysis, shorter disease duration and being negative for rheumatoid factor at the discontinuation of infliximab were found to most affect infliximab-free remission (data not shown, unpublished). Interestingly, 48% of the infliximab-free patients were negative for rheumatoid factor when infliximab was discontinued, although 77% of them were positive for it when infliximab was initiated.

It is important but difficult to determine how long preferable disease control can be sustained after discontinuing TNF inhibitors. Longitudinal observations as noted in the BeSt, TNF20, and RRR studies seem to offer some insight. In the BeSt study, the incidence of re-introduction of infliximab was reported, based on the number of risk factors according to the 8-year follow-up of infliximab-free survival in patients with early RA.[7,26] Ninety-four percent of patients who had no risk factors were sustained as infliximab-free. However, 42% of those who had 1 risk factor and 67% of those who had ≥2 risk factors needed to restart infliximab therapy. Only 2 of those who were nonsmokers and negative for anticitrullinated protein antibodies had the short treatment duration needed to re-introduce infliximab. Overall, >50% of all patients who discontinued infliximab successfully maintained DAS scores ≤2.4 for >8 years. In the 8-year follow-up of the TNF20 study in which patients with very early RA were enrolled, disease activity was significantly lower in the infliximab/MTX group than in the placebo/MTX group (median DAS28 score, 2.7 vs 4.3; $P = 0.02$).[9] Furthermore, 4 of 18 patients in the infliximab/MTX group kept DAS28 scores ≤2.6 and 1 patient achieved drug-free remission, whereas none of the placebo/MTX group remained in remission. In the RRR study, 29 of 104 patients had disease flares within 1 year (mean duration, 6.4 months) after the discontinuation of infliximab. By the 3-year follow-up, ~70% of patients failed to sustain low disease activity for 3 years after discontinuation.[26]

An advantage of a treatment holiday may be its cost-effectiveness, which includes the expected cost savings as well as quality-adjusted life-years. The BeSt study revealed that the best cost-effectiveness was observed in patients who initialized treatment with the combination therapy of MTX and infliximab among 4 treatment strategies.[27] The study found that longer quality-adjusted life-years resulted in better cost-effectiveness from both a societal and a health care perspective. This finding might be due to improved productivity that almost completely compensated for the extra medication cost as well as an increase in successful discontinuation of infliximab.

Data from animal arthritis studies indicate that the knockout mutation of TNF gene in these models reveals the amelioration of both the incidence and severity of the arthritis and that TNF is pivotally involved in the process of the disease. Because biologic agents targeting TNF substantially reduce the protein levels of TNF in the body, TNF gene–targeting models offer education on the pleiotropic bioactivity of TNF. Thus, if animal data partially reflect the efficacy of TNF inhibitors in patients with RA, it is implied that TNF inhibitors may change "the course of the disease" or induce "immunologic remission." The higher