was defined as a persistent Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate (ESR) of < 2.6 for at least 6 months. Informed consent was obtained from patients aged >18 years who had attained sustained remission with adalimumab plus MTX to discontinue adalimumab and those followed up for >6 months were evaluated. The primary endpoint was the proportion of patients who maintained sustained remission for at least another 6 months after discontinuation. DAS28, simplified disease activity index (SDAI), clinical DAI, health assessment questionnaire-disability index (HAQ-DI) and yearly progression of the modified total Sharp score (ΔmTSS) were assessed before and after discontinuation of adalimumab. To predict retaining adalimumab even after withdrawing it, a logistic regression and receiver-operating characteristic analysis were conducted on clinical variables and cut-off values at discontinuation were determined.

Of the 197 patients who started adalimumab treatment between July 2008 and April 2011 in our department, 69 (35.0%) met the criteria for sustained remission and 51 consented to enter the study. The mean age of the 51 patients was 59.5 years and mean disease duration was 7.1 years, indicating that the population included patients with long-established disease. The mean DAS28-ESR score was 5.1, implying that most patients had active disease despite MTX. Furthermore, because the mean ΔmTSS was 11.5, the addition of TNF inhibitors to MTX was needed to control joint destruction as well as disease activity. Fifty-eight percent of the evaluable 50 patients maintained adalimumab-free remission at 6 months. DAS28-ESR at discontinuation was found significantly to predict the retention of remission with a cut-off value of 2.16. Most patients (94.9%) showed no evidence of radiographic progression (ΔmTSS ≤ 0.5) at 1 year. Moreover, HAQ-DI observed at the time of adalimumab discontinuation was almost preserved at 6 months. Therefore, although the sample size is limited, the results of the HONOR study indicated that, after reaching remission with adalimumab plus MTX, most patients could discontinue adalimumab for more than 6 months without disease flare, functional impairment and radiographic damage progression. Also, deep remission at discontinuation was associated with successful biologic-free remission.

Recently, a multinational double-blind randomised controlled study was performed to determine the optimal protocol for treatment initiation with adalimumab plus MTX in patients with early RA (OPTIMA).[10] Outcomes of withdrawal or continuation of adalimumab were assessed in patients who achieved a stable low disease activity target after 26 weeks of initially assigned treatment with adalimumab and MTX. Of the 466 patients with RA treated with adalimumab plus MTX, 207 (44%) achieved stable low disease activity and were re-randomised to placebo or adalimumab plus MTX. At week 78, 86% and 66% of patients treated with adalimumab plus MTX and placebo plus MTX, respectively, achieved DAS28 remission (<2.6). SDAI remission and ΔmTSS remission were comparable for both groups.

Another trial conducted in Germany (HIT HARD) addressed the question of whether early induction therapy with a subsequent step-down strategy leads to a long-term clinical effect in patients with recent onset RA compared with initial and continued MTX monotherapy.[11] During the first 24 weeks, 172 patients were treated with adalimumab or placebo plus MTX and, after week 24, both groups were treated with MTX alone for 24 weeks. During the induction phase 47.9% of patients treated with MTX plus adalimumab achieved DAS28 remission and, at week 48, 42.4% were still in remission with 24 weeks of adalimumab-free treatment.

In the OPTIMA and HIT HARD trials, early induction therapy with adalimumab and MTX followed by withdrawal of adalimumab led to a loss of the response gained with the initial combination treatment in a subgroup of patients, but not in all patients. Unlike the HONOR study, among patients with early RA such as those in both studies, some might be capable of comprehensive disease control with initial and continued MTX monotherapy. However, the results of the HONOR study indicate that a 'treatment holiday' of biological agents by discontinuing adalimumab is now feasible in patients with RA following sustained remission, even in patients with long-standing RA encountered during routine clinical practice (figure 1).

IS DISCONTINUATION OF INFLIXIMAB POSSIBLE AFTER SUSTAINED LOW DISEASE ACTIVITY?

We also conducted a study (Remission induction by Remicade in RA patients, RRR) to examine the possibility of biologic-free remission or low disease activity in patients with RA whose mean disease duration was 5.9 years.[12] This study included a total of 114 patients with RA from 26 centres. The mean DAS28-ESR score was 5.6, implying that most patients had active disease despite MTX therapy. Furthermore, because the mean ΔmTSS was approximately 14, the addition of TNF inhibitors to MTX was needed to control disease activity and joint destruction. The patients enrolled in the study were those who had reached and maintained low disease activity (DAS28<3.2) for more than 24 weeks with infliximab treatment and who then agreed to discontinue the treatment. Among the 102 evaluable patients who completed the study, 56 (55%) maintained low disease activity after 1 year and showed no progression in radiological damage and functional disturbance, and 44 (43%) remained in clinical remission (DAS28<2.6). The mean disease duration of the group who achieved remission or low disease activity in the RRR study was 4.8±5.9 years, which made this study the first to prove that patients with long disease duration may also aim for discontinuation. Furthermore, ΔmTSS≤0.5 was observed in 67% and the HAQ-DI score was only 0.174 in patients who maintained a low disease activity for 1 year after discontinuation. We therefore conclude that more than half of patients who maintain a low disease state for more than 24 weeks on infliximab can discontinue infliximab and maintain low disease activity for a year without radiographic or functional disease progression.

The possibility of biologic-free remission in patients with RA was initially reported by a TNF20 study.[13] The combination of infliximab and MTX in patients with early RA who had symptoms for <12 months provided tight control of the disease activity. Although infliximab was withdrawn at 1 year, low clinical activity and functional abilities were sustained for another year. In the Netherlands, the Behandelstrategieën (BeSt) study was conducted to compare four treatment strategies and to observe clinical outcomes in patients with early RA (disease duration <2 years after onset, mean disease duration 0.8 years).[14–16] In this study, 508 patients with high disease activity were allocated to four groups and evaluated by DAS44 every 3 months. In patients with DAS44>2.4 (intermediate or high disease activity) a change or addition of medications was required, in those with DAS44≤2.4 (remission or low disease activity) the current medication was continued and, in patients with DAS44≤2.4 continued over 6 months, concomitant medications including infliximab were decreased and/or discontinued. In the fourth group who started infliximab, 90 of 120 patients (75%) achieved DAS44≤2.4 and

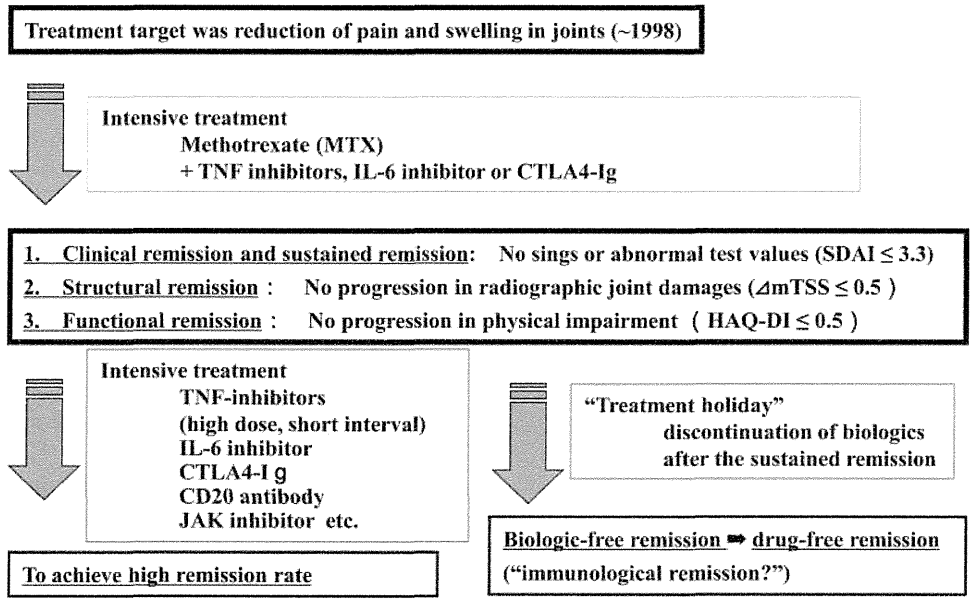

Figure 1 The next stage of the treatment of rheumatoid arthritis: intensive treatment and the possibility of a 'treatment holiday'. IL, interleukin; TNF, tumour necrosis factor.

infliximab was withdrawn in 77 cases because DAS44≤2.4 was maintained for 6 months. In the fourth group started with MTX and infliximab, the total cost of work loss and medical expenses was less than half that of the other groups started with DMARDs.

The biggest difference between the patient populations in the RRR and BeSt studies was disease duration (mean disease duration 0.8 years in the BeSt study vs 5.9 years in the RRR study), implying that biologic-free remission is possible in patients with early onset RA and also in those with long-established disease. It remains unclear whether discontinuation of biological agents targeting TNF is beneficial for comorbidity such as increased cardiovascular and/or cerebrovascular events. Since nearly a decade has passed since the BeSt study was initiated, some answers to this query may be drawn from the study.

IS TNF INVOLVED IN THE DISEASE PROCESSES?

In the BeSt study, 58% of 120 patients discontinued infliximab and 19% of patients have discontinued all DMARDs and remained in clinical remission with minimal joint damage progression 5 years after receiving infliximab and MTX as initial treatment for RA, suggesting the possibility of treatment-free remission.

In our institution, among 577 patients who were treated with infliximab, 88 patients reached biologic-free remission and only five are currently in drug-free remission without MTX. Although both TNF inhibitors and MTX play a role in the treatment, our data suggest that discontinuation of MTX appears to be difficult in patients with long-established RA. The mode of action of MTX is not discussed here, but its continuation is needed as a standard key drug. Discontinuation of biological agents benefits the economic burden of long-term management.

Accumulated studies indicate the involvement of TNF in the disease process in animal arthritis models, especially at the early stages of joint inflammation. Introduction of TNF transgene into the mouse results in typical polyarthritis, with hyperplasia of the synovium, inflammatory infiltrates in the joint space, pannus formation and cartilage and bone destruction. However, the polyarthritis and joint destruction obtained were completely ameliorated by the preventive as well as curative application of TNF inhibitors.[17] Meanwhile, TNF deficiency reduced the incidence of autoimmune arthritis in most models.[18–20] For instance, K/BxN is a model of arthritis which expresses both T cell receptor (TCR) transgene *KRN* and the MHC class II molecule *Ag7*. In the mouse, TCR recognises a self-antigen glucose-6-phosphate isomerase (GPI) and produces anti-GPI antibody, and arthritis is induced by the injection of the serum to naïve mice. Although TNF is highly expressed in K/BxN mice, deficiency of the *TNF* gene markedly reduced both the incidence and severity of the autoimmune arthritis. SKG is also an inflammatory arthritis model with a point mutation of *ZAP-70*, a member of spleen tyrosine kinase (Syk) associated with the TCRζ chain. The knockout mutation of the *TNF* gene in SKG mice showed amelioration of both the incidence and the severity of the arthritis.

If animal data partially reflect the efficacy of TNF inhibitors in patients with RA, it suggests that TNF inhibitors may change the disease course or induce immunological remission in RA. Interestingly, 48% of the 577 patients with RA described became negative for rheumatoid factor (RF) when infliximab was discontinued, although 77% of them were positive for RF at baseline when infliximab was initiated. Although the studies are limited, when the disease course is successfully changed by intensive treatment including the combination of MTX and TNF inhibitors, patients with RA may have the possibility of a 'treatment holiday' of TNF inhibitors.

CONCLUSIONS

Although the studies are limited, after reduction of disease activity to clinical remission by TNF inhibitors such as infliximab and adalimumab in combination with MTX, patients may be able to discontinue TNF inhibitors without clinical flare, radiographic progression of articular destruction and functional impairment. A 'treatment holiday' of biological agents is possible in patients with early RA and also in those with long-established RA. It has to be realised that intensive treatment with a TNF inhibitor is required to bring about the 'treatment

holiday' efficiently since deep remission was a major factor affecting the success of discontinuation of TNF inhibitors in two Japanese studies. Discontinuation of biological agents during treatment of RA has become an important area of investigation in rheumatology patients and governments from the risk-benefit viewpoint including health economic considerations. Meanwhile, because treatment with TNF inhibitors can bring about the induction of remission, sustained remission and subsequent biologic-free remission—that is, it may change or modify the course of the disease—a clinical and basic research approach to the 'process-driven disease course' of RA is warranted from wider standpoints, leading to the elucidation of pathological mechanisms and treatment strategies.

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SUPPLEMENT

Janus kinase inhibitors in autoimmune diseases

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ABSTRACT

Biological therapies directed at proinflammatory cytokines have irrevocably changed the landscape of treatment of rheumatoid arthritis (RA) and other autoimmune diseases. With the advances in our knowledge in cytokine signalling, the question emerges whether targeting intracellular signalling might also be a safe and efficacious strategy. Janus kinases or Jaks are critical for a large family of cytokines and the first Jak inhibitors has been approved by the FDA. It is therefore timely to consider this new category of drugs and reflect on their potential roles, present and future, in the treatment of RA and related disorders.

ROLE OF TYPE I/II CYTOKINES IN RHEUMATOID ARTHRITIS AND RELATED DISEASES

Cytokines are critical for host defence and immunoregulation, but also major players in the immunopathogenesis of autoimmune diseases. Practically, rheumatologists can adduce the success of recombinant cytokine receptors and monoclonal antibodies against cytokines as evidence for the immunopathological role of these factors[1] What the practising physician may be less cognisant of is the complexity of cytokines and the diversity of their structure.

Based on structure, several major families of cytokines can be recognised. Two major classes are the so-called type I and type II cytokine receptors. Type I receptors bind several interleukins (ILs), colony stimulating factors and hormones such erythropoietin, prolactin and growth hormone. Type II receptors bind interferons and IL-10 related cytokines.

Genome-wide association scans have identified a plethora of single-nucleotide polymorphisms (SNPs) conferring genetic susceptibility in autoimmune diseases such as rheumatoid arthritis (RA),[2] psoriasis,[3] inflammatory bowel disease (IBD)[4] and ankylosing spondylitis.[5] Polymorphisms of genes encoding type I cytokine receptors and their signalling elements are now firmly linked to various autoimmune diseases. For instance, *IL-23R*, *IL12B*, *JAK2* and *STAT3* polymorphisms are associated with IBD and psoriasis. *STAT4* polymorphisms are associated with RA, systemic lupus erythematosus and Sjogren syndrome. Other evidence of culpability of type I/II cytokines in autoimmunity comes from their detection in the context of disease. RA, for instance, is associated with overproduction of IL-6, IL-12, IL-15, IL-23, granulocyte-macrophage colony stimulating factor (GM-CSF) and interferons.[2]

SIGNALLING VIA TYPE I/II CYTOKINE RECEPTORS

In contrast to other receptors, whose intracellular domains encode kinase or other enzymatically active domains, these receptors lack such elements. Instead, the cytoplasmic domain of type I and II cytokine receptors binds to members of a specific kinase family, known as the Janus kinases (Jaks) which include Tyk2, Jak1, Jak2 and Jak3 (figure 1).[6] Cytokine receptors are paired with different Jaks, which are activated on cytokine binding (figure 2). Because Jaks are phosphotransferases, they catalyse the transfer of phosphate from ATP to various substrates such as cytokine receptors. This modification allows the recruitment of various signalling molecules including members of the signal transducer and activator of transcription (STAT) family of DNA binding proteins.[7] STATs are another important Jak substrate. Phosphorylation of STATs promotes their nuclear accumulation and regulation of gene expression.

Elegant work from mutagenised cell lines and later, knockout mice, supports the critical and specific role of Jaks signalling by type I/II cytokines and not other pathways.[8] In vivo evidence of the non-redundant functions in humans emerged from primary immunodeficiency patients.[9]

It is important both conceptually and practically to bear in mind that receptors for cytokines like tumour necrosis factor (TNF), IL-1 and IL-17 are structurally distinct from type I/II cytokine receptors; these cytokines are not dependent upon Jaks for signalling.[10–12]

TARGETING KINASES

Work over the past 25 years has established that protein phosphorylation is a fundamentally important mode of intracellular signal transduction.[13] Thanks to the completion of the human genome, we now know the identity of all these players: there are over 500 kinases in the human kinome, which can be divided into eight families. The Jaks belong to the tyrosine protein kinase family of which there are 90 members. Structurally, the catalytic domains of all these kinases are highly conserved. Consequently, one might imagine that generating therapeutically useful kinase inhibitors would be an enormous challenge. However, it is now clear that kinases are actually very good targets and chemists have become skilled in generating reasonably selective inhibitors. So far, 13 inhibitors have entered clinical use and are approved by the FDA. Clearly, the overall strategy of targeting kinases is no longer theoretical.

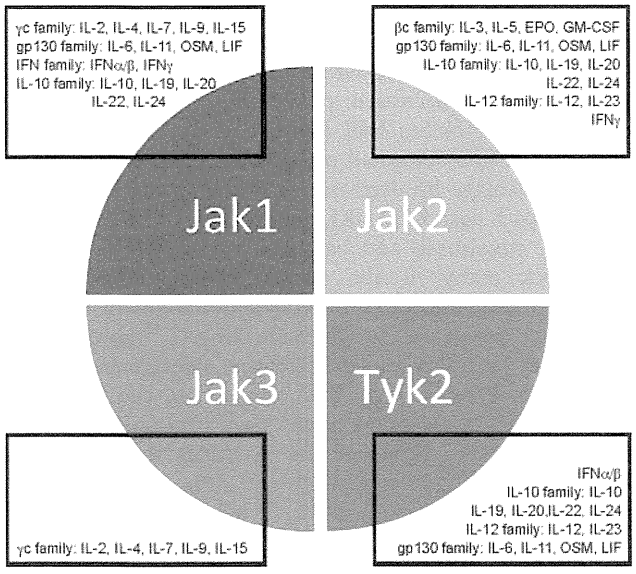

Figure 1 Usage of different Janus kinases (Jaks) by various cytokines.

JAKINIBS IN 2013

The critical function of Jaks in cytokine signalling has made them targets for industry to consider. At present there are a number of Jak inhibitors (Jakinibs) in clinical use or being tested in clinical trials.

Ruxolitinib and baracitinib

The discovery that gain-of-function *JAK2* mutations underlie the myeloproliferative disorders including polycythaemia vera, essential thrombocythemia and myelofibrosis (MF) was a great breakthrough in understanding the pathophysiology of these disorders.[14] The identification of these mutations also provided a rationale for purposefully targeting this enzyme. Ruxolitinib is a Jak1/2 inhibitor that is now approved by the FDA for the treatment of intermediate- and high-risk MF.[15–17] Ruxolitinib reduces splenomegaly and systemic symptoms and also improves overall survival.

However, ruxolitinib has also been studied in RA where preliminary results were promising in terms of efficacy and safety in a phase IIa trial.[18] Ruxolitinib has also been used as a topical formulation in psoriasis with promising results.[19] Like ruxolitinib, baracitinib (formerly designated INCB028050) is also a Jak1/Jak2 inhibitor which showed efficacy in a highly active RA patient group resistant to disease modifying drugs and biological, with superior results in higher doses up to 4 or 8 mg once daily within 2 weeks; dose dependent side effects included decrease of haemoglobin and neutrophil count and increase of low density lipoprotein (LDL) and creatinine, but there was good overall tolerability.[20]

Tofacitinib

Tofacitinib (formerly CP-690550) was actually the first Jak inhibitor to be tested in the clinic. Tofacitinib inhibits Jak3 and Jak1 and to a lesser extent Jak2. It has little effect on Tyk2.[21]

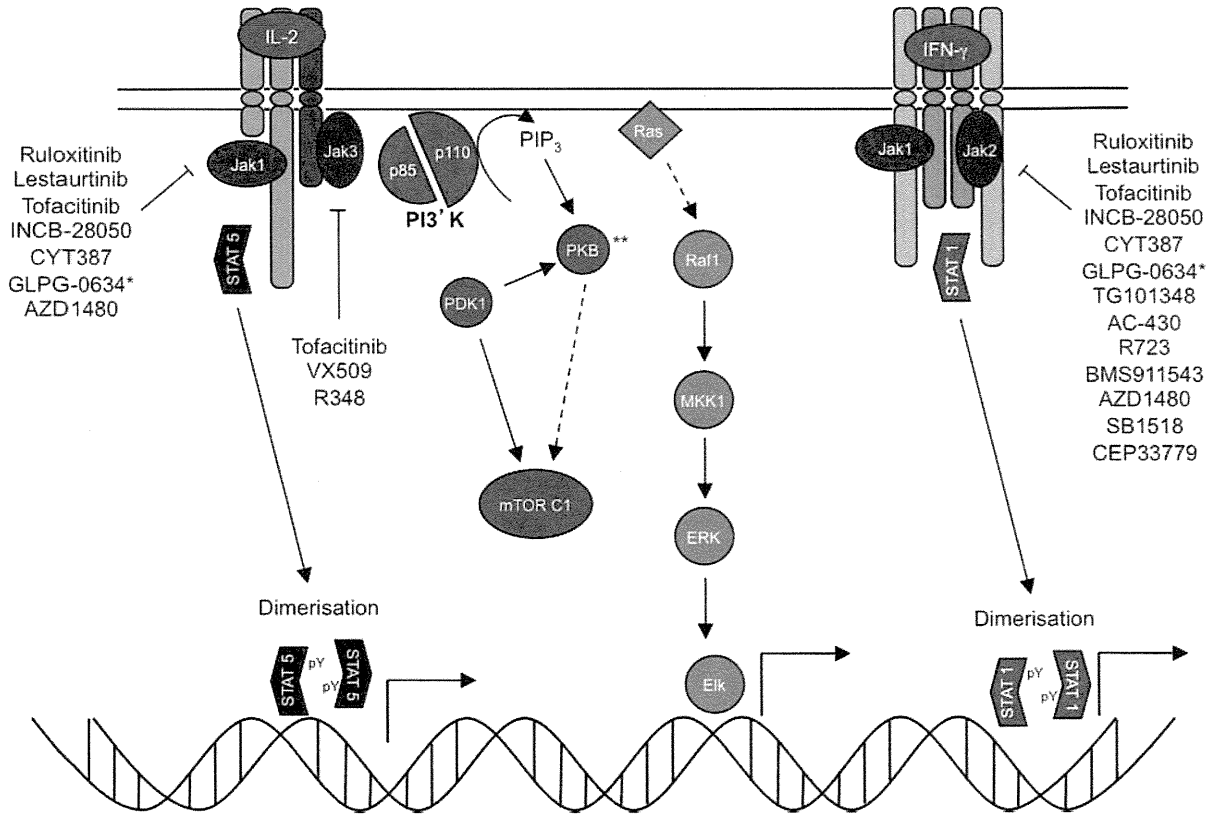

Figure 2 Janus kinase (Jak) inhibitors (Jakinibs) block multiple aspects of cytokine signalling. Cytokine binding to its cognate receptor leads to phosphorylation of the intracellular domain of the tyrosine kinase receptor by specific Jaks. Signal transducer and activator of transcriptions (STATs) are then recruited, bind to the receptor and become phosphorylated by Jaks. This results in STAT dimerisation, translocation and regulation of gene transcription. Cytokines also activate the protein kinase B (PK; also known as Akt, which is named after the Ak mouse strain that predisposes to thymoma) and mammalian target of rapamycin (mTOR). Though not carefully studied, it is highly likely that blocking proximal cytokine signals will disrupt all downstream pathways. ** Also referred to as AKT.

Across the kinome it has selectivity, remarkably sparing other kinases, showing its high specificity compared to others.[22]

Because of the prominent role of type I/II cytokines in driving autoimmunity and the effect of tofacitinib on these cytokines, this drug has been tested in a range of settings from RA, IBD and psoriasis to renal transplantation rejection and dry eyes.[23–28] Phase III trials have shown efficacy for tofacitinib in RA patients who have failed disease-modifying anti-rheumatic drugs (DMARDs), both as monotherapy[24] and in combination with methotrexate.[25] These findings are consistent with prior phase II trials.[27 29] Of interest, tofacitinib was not inferior to standard of care therapy, namely, adalimumab in combination with methotrexate[30] There is evidence that structural damage was also averted,[31] however, further investigation will be needed to substantiate this. Of note, tofacitinib was efficacious in patients who failed with multiple biologicals.[24] For all these reasons, tofacitinib has recently been approved by FDA in the USA for moderate to severe RA in patients with inadequate responses to methotrexate.

Other Jakinibs

The picture is made complicated in that VX-509, a reportedly specific Jak3 inhibitor, was also efficacious in a phase IIa study in RA.[32] Moreover, a reportedly selective Jak1 inhibitor, GLPG0634, also met its primary endpoint in a phase IIa RA trial with no anaemia and no lipid abnormalities observed.[33] CEP-33779, a selective Jak2 inhibitor, showed efficacy in two preclinical arthritis models.[34] Thus, the relative contribution of the different Jaks in disease pathogenesis and the utility of selective blockade remains to be determined. At present, there are no selective Tyk2 inhibitors in clinical trials.

MECHANISM OF ACTION OF FIRST-GENERATION JAKINIBS

An increasing body of evidence implicates specific cytokines and cell subsets as drivers of pathogenesis in different autoimmune diseases. Many of these key cytokines use the Jak/STAT pathway to exert their effects, rendering them amenable to therapeutic blockade with Jakinibs. Given the apparent pathogenic role of a variety of cytokines like IL-6, IL-12, IL-23, interferons and GM-CSF in RA, psoriasis, IBD, AS and other autoimmune diseases, the ability of Jakinibs to block such cytokines is likely a major aspect of their mechanism of action.

Mechanistically, tofacitinib blocks common γc cytokines including IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, all of which are signal through Jak3. In addition, it blocks Jak1, which would result in inhibition of the gp130 family including IL-6 and IL-11, as well as the type II cytokine receptor family such as interferon (IFN)-α/β, IFN-γ and IL-10. To a lesser extent the drug blocks Jak2 and therefore blocks the βc family such as IL-3, IL-5 and GM-CSF as well as EPO (erythropoietin) and IFN-γ.[6] Because tofacitinib blocks Jak1 and Jak2, it interferes with the differentiation of IFN-γ producing Th1 cells. It also blocks the generation of pathogenic Th17 cells, which are dependent on IL-23.[21 35] Because tofacitinib blocks IL-4 and IL-21, it might be anticipated that it will interfere with the function of B cells and follicular helper T cells. In addition to blocking the function of lymphocytes (adaptive immunity), tofacitinib also blocks innate immune responses. Specifically, tofacitinib blocks the effects IL-6 and interferons and thereby inhibits chemokine production from synovial fibroblasts.[35 36] In a sepsis model, which is dependent on IFN-γ, tofacitinib blocked the production of TNF and IL-1.[21] Thus, tofacitinib can interfere with the production and action of TNF. However, TNF signalling per se is not affected; rather, tofacitinib blocks autocrine effects of interferons that mediate TNF effects.[36] In patients with RA treated with tofacitinib, serum levels of IL-6 were significantly decreased; presumably, this is due to effects on type I/II cytokines that induce IL-6.[37] In an RA animal model, tofacitinib abrogated osteoclast-mediated arthritic joint structural damage by decreasing receptor activator of nuclear factor kappa-B ligand (RANKL) production.[38]

Because ruxolitinib and baracitinib inhibit Jak1 and Jak2, they block many of the same cytokines as tofacitinib. Deletion of Jak3 impedes lymphocyte development because of its requisite role in cγc cytokine signalling.[39–41] However, gene targeting of Jak1 also results in a severe combined immunodeficient phenotype.[42] From this perspective, the expectation would be that these drugs might have very similar mechanisms of action, in terms of the cytokines that are blocked (figure 2).

SIDE EFFECTS OF JAKINIBS

An important side effect of Jakinibs is serious bacterial, mycobacterial, fungal and viral infections. In the phase II, III and long extension trials of tofacitinib among opportunistic infections, tuberculosis (TB) was reported in 12 cases, 11 of which were initially negative on screening for TB, and 10 occurred in patients from endemic countries. Increased frequency of non-disseminated herpes zoster was also reported which may reflect reduction of NK cells by virtue of Jak1 or Jak3 blockade. Whether this accounts for viral infection susceptibility remains to be established. Longer duration adequately powered trials are needed to estimate the risk of common and opportunistic infections. A potential advantage of Jakinibs compared to biologicals with respect to infection risk is the relatively short half-life of the former; if infections occur, the drug can be stopped and the immunomodulatory effect is transient.

Jakinibs can cause anaemia, thrombocytopenia and neutropenia, likely related to Jak2 inhibition, which is important for EPO signalling and the actions of colony stimulating factors. When used for treatment of MF in the setting of thrombocytopenia, the dose of ruxolitinib needs to be adjusted accordingly.

Use of Jakinibs is associated with hypercholesterolaemia. However, this is also consistently observed in RA trials with tocilizumab, implying that high LDL, triglycerides and high density lipoprotein may be mediated by blockade of IL-6 signalling. Standard anti-hyperlipidaemic therapy improves the metabolic profile but the overall risk for cardiovascular morbidity will need to be determined in the long term.[43]

Small increases in creatinine have been observed with tofacitinib; it is unclear if these effects are related to the drug's mechanism of action.

A concern regarding chronic treatment with Jakinibs pertains to the possibility of increased cancer risk. Interferons and NK cells are important in tumour surveillance and the blockade of their action provides the theoretical rationale for development of malignancies mandating increased clinical vigilance.[44] The rate of lymphomas or other lymphoproliferative disorders in phase III and long extension studies of tofacitinib in RA was 0.07 per 100 patient-years (95% CI 0.03 to 0.15) which is comparable with studies of other biologicals and the general RA population.[25]

Overall, the use of Jakinibs in clinical practice depends on the efficacy and safety ratio compared to standard of care therapy in a carefully selected patient population.

THE FUTURE OF JAKINIBS IN TREATING AUTOIMMUNE DISEASE

Clinical use of Jakinibs

Over the past decade, the biologicals have clearly raised the bar with respect to treatment of rheumatic disease. They are highly effective and remarkably safe. However, not all patients respond. Exactly how Jakinibs will fit within the rheumatologist's armamentarium remains to be seen. It will be of interest to see how a new, highly effective oral agent will be embraced relative to established parenteral drugs. An exciting development is that patients who fail with biologicals respond to Jakinibs.

Jakinibs in other diseases

Trials in psoriasis, IBD and transplantation are presently ongoing. In preclinical studies, Jakinibs appear to have efficacy in lupus models.[34 45 46] The possibility of treating patients with systemic lupus erythematosus is attractive given the prominence of the 'interferon signature' in this disease.[47–49] Asthma and allergy is associated with Th2 responses and the action of IL-4. Jak1 and Jak2 are important for IL-4 signalling and the potential utility of tofacitinib and other Jakinibs in these disorders is supported by preclinical data.[50]

Selective versus pan-Jak inhibitors

The kinome is a known entity—so for any new kinase inhibitor it is a fair question to ask what its selectivity is. Does it inhibit just Jaks or other kinases as well? How specific is it among the Jaks? These are important questions for any new drug coming along in order to understand its mechanism of action but also its side effects. The present Jakinibs all block more than one Jak, so all inhibit multiple cytokines. The question going forward is whether more selective Jakinibs will be as effective and potentially safer. While one might assume that more selectivity would be better, this assumption is not always borne out. Just look at the experience with non-steroidal anti-inflammatory drugs and selective Cox2 inhibitors. Another possible scenario is that multikinase inhibitors might be useful in early phases of disease treatment, when a plethora of inflammatory responses are raging. Later, when disease is more controlled, perhaps a more selective inhibitor might be safe and effective for maintenance therapy.

Lessons learned?

Thanks to the completion of the human genome, there are hundreds of potential therapeutic targets for autoimmune disease. And yet, the cost of generating a new drug typically runs to a billion or so dollars. The development of Jakinibs will surely be studied to see if there are lessons that might be gleaned for other classes of new drugs. In contrast to initial views, kinases turn out to be very 'druggable' and genetic information unequivocally established the requisite function of Jaks in cytokine signalling. However, knocking out *Jak2* in mice resulted in embryonic lethality, so one might have thought that a drug with Jak2 activity would be problematic. It is clear that equating drugs to knockouts is not always useful. If Jaks are good targets, one might imagine that STATs would also be good targets; however, targeting the latter has proven to be extremely difficult.

CONCLUSIONS

The development of kinase inhibitors has offered new therapies for diverse clinical entities ranging from malignancy to autoimmunity. Jak inhibitors or Jakinibs initially launched to treat a rare haematological disorder are now progressing to be used in not only malignancies but common autoimmune disorders as well. The role of Jak inhibitors in the treatment algorithm of diseases ranging from the vasculitides to systemic lupus erythematosus or polymyalgia rheumatica remains to be determined. Where Jakinibs will fit in the spectrum of therapeutic options from DMARDs and steroids to biologicals and cyclophosphamide is unknown. However, the excitement is that if approved, Jakinibs will be the first new approved oral therapy for RA in a decade.

Competing interests JJO'S and the National Institutes of Health (NIH) hold patents related to targeting JAKs as targets for immunomodulatory agents. JJO'S and the NIH have a Collaborative Research Agreement and Development Award with Pfizer.

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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 in-Duction 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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A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study

In terms of the relationship between synovial inflammation and radiographic changes, including both joint damage repair and progression,[1] in rheumatoid arthritis (RA), pre-existing joint damage and persistent synovitis may promote joint destruction, while in the absence of synovitis, damaged joints may heal.[2 3] Although presentation of radiographic results using cumulative probability plots has substantially improved understanding of clinical trial data,[4] the effects of treatments on radiographic progression and improvement (regression) in individual RA patients has not yet been fully explained.

In the JESMR study,[5 6] 151 active RA patients unresponsive to treatment with methotrexate (MTX) were randomised into 1 of 2 treatment groups: etanercept (ETN) 50 mg/week with 6–8 mg/week of MTX (the E+M group), or ETN alone (the E group). Radiographs of the hands and feet before ETN (baseline) and during the first year of treatment were available from 53 (72%) and 68 (88%) patients in the E and E+M groups, respectively. Baseline characteristics of patients were comparable between those with and without available radiographic data in each treatment group (data not shown). However, most patients without data did not complete the study up to Week 52 as per protocol, chiefly due to lack of efficacy in the E group.[6] The mean baseline total Sharp-van der Heijde score (TSS)[7] was 114.5 in the E group and 113.1 in the E+M group (disease duration: 10.0 years and 8.4 years, respectively), and the smallest detectable change (SDC) in TSS over 52 weeks was 1.9.

Cumulative probability plots provided by the American College of Rheumatology (ACR)-N[8] clearly demonstrated a superior response (figure 1A,B) and a significantly greater ACR50 response rate in the E+M group at week 52 (76.5% vs 50.9%, p=0.0041, Fisher's exact test). Merged probability plots of individual radiographic change over 52 weeks (ΔTSS) suggested preferential existence of aggressive radiographic progressors among ACR50 non-responders in the E group. The relationship among treatment, clinical disease activity, and radiographic change was further addressed using time-averaged disease activity score of 28 joints (DAS28) over 52 weeks in place of ACR-N at Week 52 (figure 1C,D). Significant correlation between time-averaged DAS28 and ΔTSS was observed in the E (r^2=0.097, p=0.023) but not the E+M group (r^2=0.019, p=0.26). Aggressive radiographic progression was preferentially observed among patients with moderate or high activity on average in the E group (figure 1C), while in the E+M group, radiographic progression among these patients seemed to be balanced by radiographic regression among those in remission or with low disease activity (figures 1D–F).

The absence of radiographic regressors (>SDC) among clinical responders in the E group (figure 1A,C,E) was surprising, although 18.2% of those patients showed regression within the SDC. This may be partly explained by the limitations of the study due to the small number of patients involved. Another limitation was much lower MTX dose at study enrolment than the current global standard dosage: 7.0±1.4 (the mean±SD) and 7.4±1.1 in the E and E+M groups, respectively.

In summary, we first demonstrated the relationship between individual clinical responses and radiographic changes by merging cumulative probability plots of ACR-N or time-averaged DAS28 and ΔTSS. These presentations clearly show the relationships between two parameters as a whole, facilitating further post hoc analyses of clinical trials. Further, merged presentation of probability plots is useful in comparing a single parameter (eg, health assessment questionnaire-disability index: HAQ-DI) before and after treatments (figure 2). However, merged presentation of probability plots must be followed by statistical analyses after being classified into binary or ternary categories, as we showed here.

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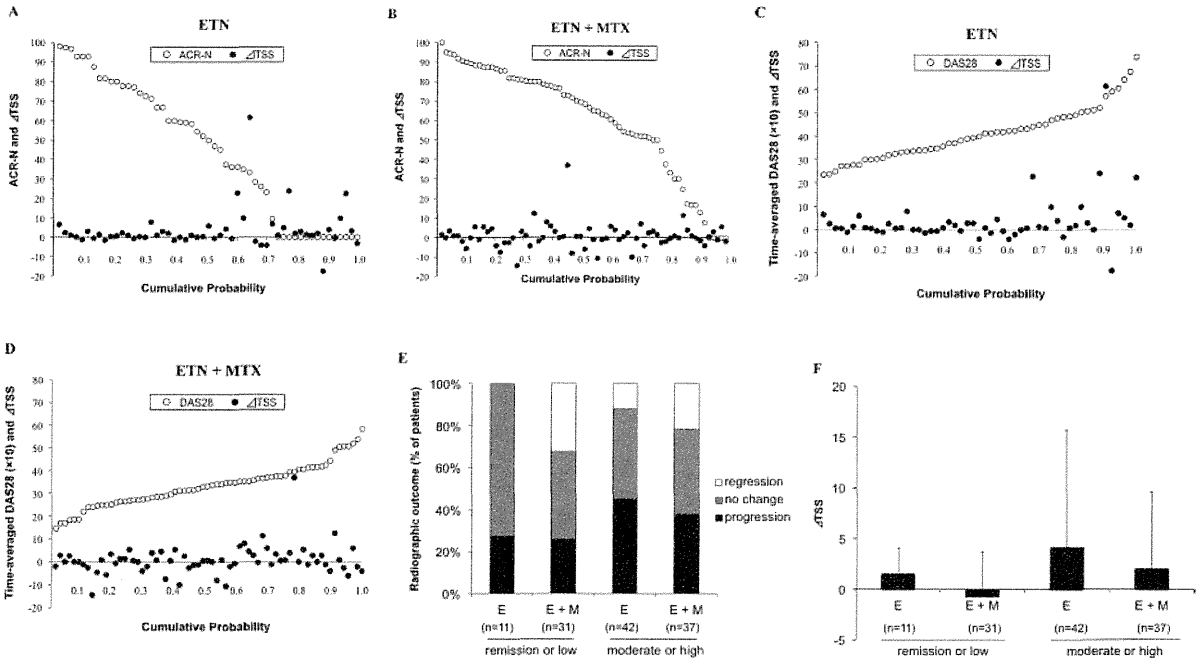
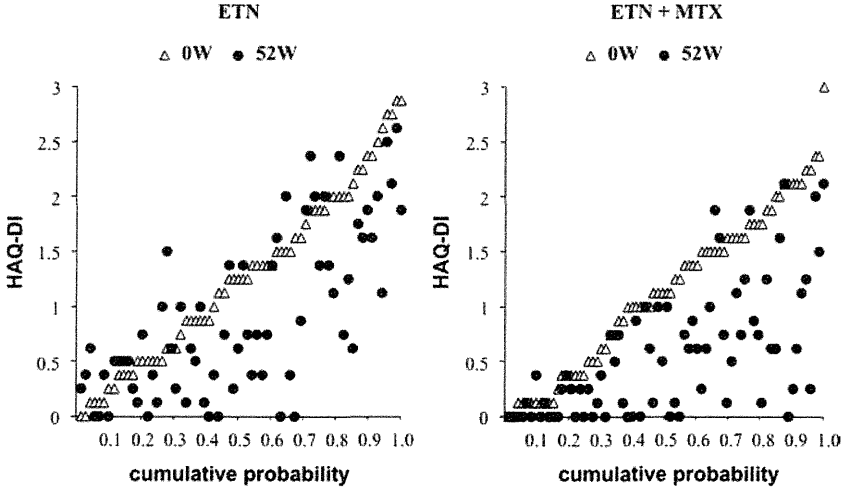


Cumulative probability plot analysis of ACR-N (A,B) or time-averaged DAS28 (C,D) and radiographic changes in the E (A,C) and E+M groups (B,D), merged to keep same patients on the vertical line, followed by the radiographic outcomes (E) and changes (F) stratified by the treatment and time-averaged disease activity state. Time-averaged DAS28 was calculated by the area under the curve of DAS28 at weeks 0, 2, 4, 8, 12, 24 and 52, divided by 52. No significant differences were observed between groups using Pearson's test (E) and Kruskal-Wallis test (F). ACR, American College of Rheumatology; DAS28, disease activity score of 28 joints; ETN, etanercept; MTX, methotrexate; TSS, total Sharp-van der Heijde score.



Merged probability plots of individual health assessment questionnaire-disability index (HAQ-DI) scores at baseline (open triangle) and Week 52 (closed circle) in the E (left) and E+M groups (right). Subsequent analyses included comparison of the rate of HAQ-DI≤0.5 at 52 weeks in patients with baseline HAQ-DI>1.5. None of 15 patients (0.0%) in the E group and 6 of 23 patients (26.1%) in the E+M group, respectively; p=0.037 by Fisher's exact test (one-sided). ETN, etanercept; MTX, methotrexate.

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Tofacitinib (CP-690,550) in Patients With Rheumatoid Arthritis Receiving Methotrexate

Twelve-Month Data From a Twenty-Four–Month Phase III Randomized Radiographic Study

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Objective. **The purpose of this 24-month phase III study was to examine structural preservation with tofacitinib in patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX). Data from a planned 12-month interim analysis are reported.**

Methods. **In this double-blind, parallel-group, placebo-controlled study, patients receiving background MTX were randomized 4:4:1:1 to tofacitinib at 5 mg twice daily, tofacitinib at 10 mg twice daily, placebo to tofacitinib at 5 mg twice daily, and placebo to tofacitinib at 10 mg twice daily. At month 3, nonresponder placebo-treated patients were advanced in a blinded manner to receive tofacitinib as indicated above; remaining placebo-treated patients were advanced at 6 months. Four primary efficacy end points were all analyzed in a step-down procedure.**

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Results. **At month 6, response rates according to the American College of Rheumatology 20% improvement criteria for tofacitinib at 5 mg and 10 mg twice daily were higher than those for placebo (51.5% and 61.8%, respectively, versus 25.3%; both $P < 0.0001$). At month 6, least squares mean (LSM) changes in total modified Sharp/van der Heijde score for tofacitinib at 5 mg and 10 mg twice daily were 0.12 and 0.06, respectively, versus 0.47 for placebo ($P = 0.0792$ and $P \leq 0.05$, respectively). At month 3, LSM changes in the Health Assessment Questionnaire disability index score for tofacitinib at 5 mg and 10 mg twice daily were −0.40 (significance not declared due to step-down procedure) and −0.54 ($P < 0.0001$), respectively, versus −0.15 for placebo. At month 6, rates of remission (defined as a value <2.6 for the 4-variable Disease Activity Score in 28 joints using the erythrocyte sedimentation rate) for tofacitinib at 5 mg and 10 mg twice daily were 7.2% (significance not declared due to step-down procedure) and 16.0% ($P < 0.0001$), respectively, versus 1.6% for placebo. The safety profile was consistent with findings in previous studies.**

Conclusion. **Data from this 12-month interim analysis demonstrate that tofacitinib inhibits progression of structural damage and improves disease activity in patients with RA who are receiving MTX.**

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease characterized by inflammation and destruction of the joints, substantial disability, and a significant impact on health status and quality of life. This results in a substantial economic burden to patients and society (1).

Tofacitinib (CP-690,550) is a novel JAK inhibitor being investigated as a targeted immunomodulator and disease-modifying therapy in RA (2,3). In kinase assays, tofacitinib inhibits JAK-1, JAK-2, and JAK-3, and to a lesser extent tyrosine kinase 2; in cellular settings, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK-3 and/or JAK-1 with functional selectivity over JAK-2–paired receptors. Inhibition of JAK-1 and JAK-3 by tofacitinib blocks signaling through the common γ-chain–containing receptors for several cytokines, including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 (3,4), which are integral to lymphocyte function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

In phase IIb dose-ranging studies that evaluated a dose range of 1–15 mg twice daily, tofacitinib demonstrated sustained efficacy and manageable safety over 24 weeks in patients with active RA when used as monotherapy (5) or in combination with background methotrexate (MTX) (6). Tofacitinib doses of 5 and 10 mg twice daily were selected as optimal for evaluation in phase III, which includes a broad range of therapeutic scenarios investigating tofacitinib as monotherapy (7) or in combination with MTX (8–10) and non-MTX nonbiologic disease-modifying antirheumatic drugs (DMARDs) (11).

The purpose of this phase III study was to examine structural preservation, improvements in signs and symptoms of RA, and physical function, and to evaluate safety and tolerability with tofacitinib at 5 and 10 mg twice daily over 24 months in adult patients with active RA with an inadequate response to MTX. Data from a planned 12-month interim analysis of this study are reported here.

PATIENTS AND METHODS

Patients. Eligible patients were age ≥18 years with a diagnosis of active RA based on the American College of Rheumatology (ACR) 1987 revised criteria (12). Active disease was defined by ≥6 tender/painful joints (68-joint count) and ≥6 swollen joints (66-joint count) and by an erythrocyte sedimentation rate (ESR) (Westergren method) of >28 mm/hour or a C-reactive protein level of >7 mg/liter (reference range 0–10 mg/liter). Patients were also required to have evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM rheumatoid factor (RF) positivity or antibodies to cyclic citrullinated peptide (anti-CCP). Stable doses of MTX were required (15–25 mg weekly for ≥6 weeks; stable doses <15 mg were allowed only if there were safety issues at higher doses). Stable doses of low-dose corticosteroids (≤10 mg/day prednisone or equivalent) and nonsteroidal antiinflammatory drugs (NSAIDs) were allowed. Prior use of biologic or nonbiologic DMARDs was permitted.

Key exclusion criteria were hemoglobin <9.0 gm/dl, hematocrit <30%, white blood cell count $<3.0 \times 10^9$/liter, absolute neutrophil count $<1.2 \times 10^9$/liter, or platelet count $<100 \times 10^9$/liter; estimated glomerular filtration rate ≤40 ml/minute (Cockcroft-Gault calculation); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >1.5× the upper limit of normal (ULN); recent, current, or chronic infection, including hepatitis B or C or human immunodeficiency virus; evidence of active, latent, or inadequately treated *Mycobacterium tuberculosis* infection; or history of lymphoproliferative disorder or malignancy except for adequately treated nonmetastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ.

Study design and treatment. This was a phase III, randomized, double-blind, parallel-group, placebo-controlled study (Pfizer protocol A3921044) in 111 centers in North America, South America, Europe, Asia, and Australia with the first visit of the first patient on March 31, 2009; this analysis

includes all patients' 12-month data with the last visit of the last patient on April 1, 2011. A list of the ORAL Scan trial (Oral Rheumatoid Arthritis triaL A3921044) study investigators is provided in Appendix A. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice in the European Community, and local country regulations. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards and the Independent Ethics Committees of the investigational centers. All patients provided written, informed consent.

Using an interactive voice recognition system, patients were randomized 4:4:1:1 to 1 of 4 sequences: tofacitinib at 5 mg twice daily, tofacitinib at 10 mg twice daily, placebo to tofacitinib at 5 mg twice daily, and placebo to tofacitinib at 10 mg twice daily, all in combination with MTX. For ethical reasons, patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months (defined as nonresponders) were advanced in a blinded manner to their predetermined dose of tofacitinib as indicated above. All patients continuing to receive placebo were advanced in a blinded manner to tofacitinib after 6 months. A nonresponder patient randomized to tofacitinib was also advanced in a blinded manner but continued to receive the same treatment and dose for the duration of the study. Increases in NSAIDs and systemic corticosteroids were not permitted; decreases were allowed only if required to protect patient safety.

Efficacy assessments. Coprimary efficacy end points evaluated tofacitinib at 5 or 10 mg twice daily versus placebo with respect to the response rates according to the ACR 20% improvement criteria (ACR20 response rates) (13) (at month 6), the mean change from baseline in total modified Sharp/van der Heijde score (SHS) (14) (at month 6), the mean change from baseline in the Health Assessment Questionnaire disability index (HAQ DI) score (15) (at month 3), and rates of remission, defined as a 4-variable Disease Activity Score in 28 joints using the ESR (DAS28-ESR) <2.6 (16) (at month 6). Key secondary end points included ACR20, ACR50, and ACR70 response rates and DAS28-ESR assessments (at all visits) and changes from baseline in the ACR core set of disease activity measures (17) (at month 6). Key secondary end points for structural preservation included rates of nonprogressors (≤0.5 unit change from baseline in total SHS or erosion score) (18) (at months 6, 12, and 24), changes from baseline in total SHS (at months 12 and 24), and changes from baseline in erosion score and joint space narrowing (JSN) score (at months 6, 12, and 24). Patient-reported outcomes were assessed throughout and included, in addition to the HAQ DI score, the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (19) and the patient's assessment of arthritis pain (on a visual analog scale) (15).

Radiographic methods. Radiographs for each patient were scored by 2 independent readers (who were blinded to patient randomization sequence and visit) according to the total SHS (14). The 2 readers' scores for each patient were averaged and used for the final score.

Safety assessments. Safety end points included incidence and severity of clinical laboratory abnormalities and vital signs and of all adverse events (AEs). A Cardiovascular Safety Endpoint Adjudication Committee (all external independent consultants), blinded to treatment group assignment, reviewed all potential cardiovascular events and deaths.

Statistical analysis. Sample size was determined based on structural progression (total SHS) (see Supplementary Appendix 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract). The full analysis set was the primary analysis population for efficacy and safety. This included all randomized patients who received ≥1 dose of study drug and had ≥1 postbaseline measurement (including safety data). If the end point was a change from baseline, a baseline measurement was needed. The normal approximation for difference in binomial proportions was used to test superiority of each tofacitinib dose against placebo with respect to ACR20 response rate and rates of DAS28-ESR <2.6; nonresponder imputation (NRI; setting the ACR20 response rate or the rate of DAS28-ESR <2.6 to nonresponsive) addressed missing data. NRI was applied to patients who discontinued for any reason and to patients who, at month 3, had not achieved a 20% improvement in tender and swollen joint counts regardless of treatment assignment; this analysis therefore assumed that nonresponder patients at month 3 were those for whom treatment had failed for the remainder of the study, even if they subsequently fulfilled the ACR20 criteria.

Thus, the primary analysis used NRI at month 6; as a secondary analysis and to account for tofacitinib-treated patients who "advanced" at month 3 (because of lack of meeting the response criteria) to the same dose of tofacitinib, an NRI "without an advancement penalty" was employed. This allowed assessment of clinical changes in these patients at month 6 who were receiving a stable dose of tofacitinib since day 1. The primary analysis was more conservative than it has been historically applied (NRI alone), since in order to be counted as having achieved an ACR20 response at month 6 in the primary analysis, patients are first required to have a 20% improvement in both tender and swollen joint counts at month 3. For further details of the NRI analysis, see Supplementary Appendix 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37816/abstract.

For total SHS, the primary analysis was an analysis of variance model for change from baseline to month 6, and included baseline total SHS as a covariate. A patient must have had ≥1 postbaseline radiograph to be included in the linearly extrapolated analysis. Patients who advanced before month 6 (nonresponders) had their month 6 measurements imputed using a linear extrapolation from month 3 radiographs even when month 6 radiographs were available, regardless of treatment assignment. Since all placebo-treated patients advanced by or at month 6, placebo data for month 12 were imputed using linear extrapolation from month 3 or month 6 radiographic scores, whichever was the last month at which placebo was dosed before advancement to tofacitinib. The approach of using month 3 radiographs for linear extrapolation for all treatment groups for advanced patients is similar to applying the NRI advancement penalty to all treatment groups, and is used to treat tofacitinib- and placebo-treated groups the same way in the analysis and not introduce bias in favor of tofacitinib. All total SHS–related variables were imputed using this method. Associated binary variables (e.g., rates of patients