to control the stability of mRNA.[37,38] However, dysregulated and persistent expression of IL-6 has been implicated in the development of various autoimmune diseases, chronic inflammatory diseases, and even cancers; the IL-6 signal pathway could therefore be an appropriate target for the treatment of such diseases.[39] Inhibition of this function of IL-6 consists of four strategies—inhibition of any of IL-6, IL-6R, gp130, or the cytoplasmic signaling cascade via gp130. The humanized anti-IL-6R monoclonal Ab, tocilizumab (TCZ),[40] is the first drug that successfully blocks the IL-6 signal and has been approved worldwide for the treatment of RA.

Tocilizumab, a Humanized Anti-IL-6 Receptor Monoclonal Antibody

TCZ blocks IL-6-mediated signal transduction by inhibiting IL-6-binding to transmembrane and soluble IL-6R. If concentration of free TCZ is maintained at more than 1 μg/mL, CRP remains negative[41] and the serum CRP level becomes a hallmark for in vivo confirmation of whether IL-6 activity is completely blocked. TCZ is currently approved for the treatment of RA in more than 90 countries, for the treatment of systemic juvenile idiopathic arthritis (JIA) in Japan, India, the EU, and the USA, and of polyarticular JIA and Castleman's disease in Japan and India.[42–44] For RA, the recommended TCZ posology is 8 mg/kg once every 4 weeks in Japan and the EU. The recommended starting dose in the USA is 4 mg/kg once every 4 weeks, followed by an increase to 8 mg/kg, depending on clinical response. TCZ is used for the treatment of Castleman's disease and systemic JIA at 8 mg/kg once every 2 weeks in Japan, while in the USA the recommended TCZ dosing for systemic JIA patients weighing less than 30 kg is 12 mg/kg and 8 mg/kg for those weighing more than 30 kg, intravenously once every 2 weeks.

Efficacy and Safety of Tocilizumab for Rheumatoid Arthritis

RA is an inflammatory arthritis which causes joint destruction. Inflammatory cytokines including IL-6 play an important role in the pathogenesis of RA; treatment options which inhibit IL-6 activity for patients with RA have advanced significantly over the past decade. Among these, TCZ is the first approved IL-6 signaling inhibitor.

The key mechanism by which TCZ affects RA is thought to be interference with systemic inflammation, which can normalize imbalance in the effector CD4-positive T cell subsets that generate autoimmune reactions. Interestingly, IL-6 blockade inhibits arthritis in type II collagen-induced arthritis (CIA), which requires the presence of CD4-positive T cells, and leads to the production of antitype II collagen IgG.[45] It does not, however, inhibit the development of antitype II collagen Ab-induced arthritis (CAIA), which skips the priming phase of T cell-dependent Ab generation.[46] These observations suggest that IL-6 is required primarily for the activation of T cell responses, as well as the production of Abs specific to joint components (the priming phase).[47] TCZ has little effect on spondyloarthritides such as psoriatic arthritis and ankylosing spondylitis,[48,49] for which the autoimmune process appears not to be required. Additionally, the onset of the anti-arthritic effect of TCZ is slow compared with that of TNF inhibitors. These observations suggest that TNF contributes to local inflammation, a direct cause of joint destruction, and IL-6 mainly contributes to immune activation, synovitis, and systemic inflammation (Fig. 4).

The efficacy of TCZ on RA was evaluated in seven major phase III clinical trials. Its efficacy was found to be outstanding for RA patients either as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs).[42,43] The efficacy of TCZ administered alone or in combination with methotrexate (MTX) was also confirmed for RA patients of various backgrounds. The results of these trials are summarized in Table 1. The findings of three phase III trials of TCZ monotherapy have been reported. The AMBITION trial was performed with MTX- or biologic-naïve patients,[50] the SAMURAI trial with patients with an inadequate response to DMARDs,[51] and the SATORI trial with patients with an inadequate response to MTX.[52] These studies showed that TCZ monotherapy is better than MTX and DMARD monotherapy for patients who are naïve to MTX and other biologics and that it is also effective for those who are resistant to MTX and other DMARDs. All studies showed that after 24 weeks patients treated with TCZ showed superior ACR20 (American College of Rheumatology) responses and reduction in disease activity score 28 (DAS28) when compared to controls treated with MTX or other DMARDs.[50–52]

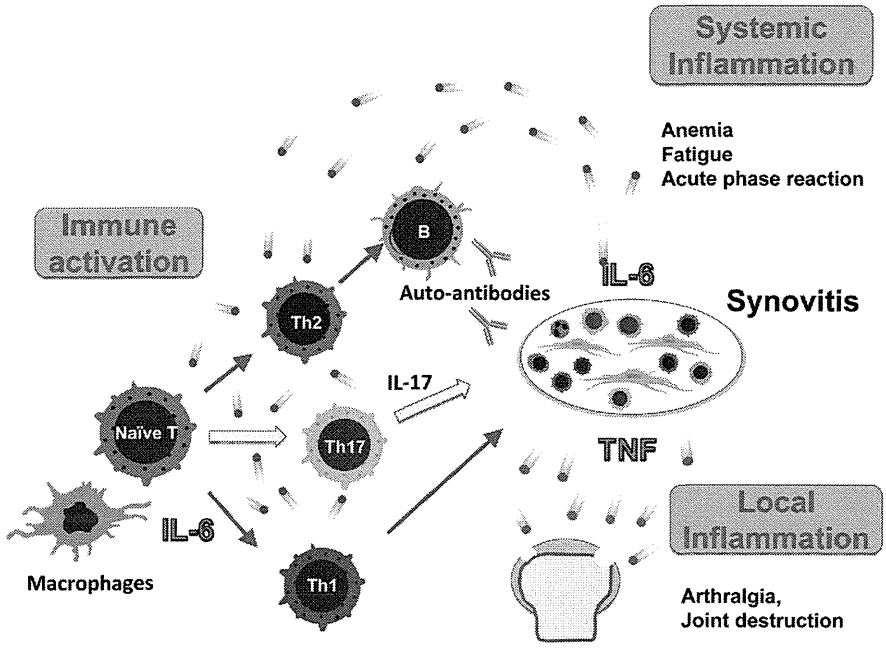

Figure 4. Pathological role of IL-6 in rheumatoid arthritis.
Notes: IL-6 is essential for the development of Th17 and induction of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibody. Activated Th17 cells and autoantibodies in combination with activated fibroblastic synoviocytes, macrophages, and lymphocytes generate pannus. Inflamed synovitis, such as those seen in pannus, is a major source of inflammatory cytokines (including IL-6); systemic inflammation, leading to production of acute-phase proteins, anemia, and fatigue, is also mediated primarily by IL-6. Tumor necrosis factor (TNF) plays a major part in the progression of local types of inflammation (arthritis) such as arthralgia, swelling, and joint destruction, but only a minor part during the priming phase.

In addition, four phase III trials of TCZ combination therapy have been performed. The OPTION trial was designed to evaluate the efficacy of TCZ in combination with MTX and showed that TCZ combination therapy was effective for and well tolerated by patients with moderate-to-severe active RA and with an inadequate response to MTX.[53,54] The TOWARD trial, with an enrollment of 1,220 RA patients, demonstrated that TCZ combined with DMARDs such as MTX, chloroquine, gold, sulphasalazine, azathioprine, and leflunomide was effective for reducing RA disease activity in patients with an inadequate response to monotherapy with any one of the DMARDs.[55] The RADIATE trial proved that TCZ plus MTX was effective for achieving rapid and sustained improvements in signs and symptoms of patients with RA refractory to TNF inhibitors; it also showed that it had a manageable safety profile.[56] The LITHE trial, which was designed to evaluate not only disease activity but also structural joint damage, demonstrated that TCZ plus MTX was effective for the suppression of disease activity and symptoms. The LITHE trial also showed that at 52 weeks TZ plus MTX significantly inhibited radiographic progression for patients with an inadequate clinical response to MTX.[57,58] In short, all these studies enrolled patients with an inadequate response to all previous treatments—including MTX, TNF inhibitors, and other DMARDs—and all showed that TCZ combination therapy was effective for these populations. In addition, the OPTION, RADIATE, and LITHE studies reported that the efficacy of TCZ was dose dependent (4 mg/kg and 8 mg/kg).[53,56,57]

Recently many phase IIIb/IV studies have been conducted in clinical settings as well. The ACT-RAY trial compared TCZ plus MTX therapy with TCZ monotherapy in a setting that closely resembled real-life clinical practice.[59] The trial was a double-blind, 2-year study in which active RA patients being treated with MTX were randomly assigned either to continue MTX with the addition of TCZ 8 mg/kg every 4 weeks or to switch to TCZ plus placebo. Of 556 randomly assigned patients, 512 (92%) completed 24 weeks. ACR20/50/70 response rates were 71.5%/45.5%/24.5% for the TCZ plus MTX group and 70.3%/40.2%/25.4% for the TCZ plus placebo group. TCZ plus MTX combination therapy was therefore shown not to be

Table 1. Summary of phase III clinical trials of tocilizumab in rheumatoid arthritis.

Study	Population	Day at evaluation	Treatment arms	Patient number	Response rate (%)	Remission rate (%)	Radiological progression from baseline
					ACR20	DAS28 < 2.6	Δ TSS
AMBITION	MTX, TNFi-naïve	24 W	TCZ (8 mg/kg)	286	70	34	
			MTX	284	53	12	
SAMURAI	DMARDs-IR	52 W	TCZ (8 mg/kg)	157	78	59	2.3
			DMARDs	145	34	3	6.1
SATORI	MTX-IR	24 W	TCZ (8 mg/kg)	61	80	43	
			MTX	64	25	2	
TOWARD	DMARDs-IR	24 W	TCZ (8 mg/kg) + DMARDs	803	61	30	
			DMARDs	413	25	3	
RADIATE	TNFi-IR	24 W	TCZ (4 mg/kg) + MTX	161	30	8	
			TCZ (8 mg/kg) + MTX	170	50	30	
			MTX	158	10	2	
OPTION	MTX-IR	24 W	TCZ (4 mg/kg) + MTX	186	48	13	
			TCZ (8 mg/kg) + MTX	191	59	27	
			MTX	189	26	1	
LITHE	MTX-IR	52 W	TCZ (4 mg/kg) + MTX	394	47	30	0.34
			TCZ (8 mg/kg) + MTX	398	56	47	0.29
			PBO	393	26	8	1.13

Abbreviations: MTX, methotrexate; TCZ, tocilizumab; IR, inadequate response; DMARDs, disease-modifying antirheumatic drugs; TNFi, TNF inhibitor; PBO, placebo; ACR20, ACR criteria for 20% improvement; DAS28, disease activity score 28; TSS, total sharp score.

clinically superior to TCZ monotherapy. The ACT-SURE trial was a phase IIIb, open-label, single-arm, 6-month study which was conducted with a patient population resembling one to be expected in clinical practice.[60] Patients, who were categorised as TNF inhibitor-naïve (never received TNF inhibitor), TNF inhibitor-previous (washout: TNF inhibitor therapy discontinued for more than 2 months) or TNF inhibitor-recent (TNF inhibitor discontinued for less than 2 months), received open-label TCZ 8 mg/kg every 4 weeks, with or without DMARDs, for 24 weeks. Overall, 1,681 (976 TNF inhibitor-naïve, 298 TNF inhibitor-previous, and 407 TNF inhibitor-recent) patients were treated. ACR20/50/70 rates by week 24 were 70.5%/51.9%/31.8%, 60.7%/35.2%/17.8% and 62.7%/42.3%/19.7% for TNF inhibitor-naïve patients, TNF inhibitor-previous, TNF inhibitor-recent patients, respectively. The ACT-STAR study was a 24-week, prospective, open-label study conducted in the USA.[61] Of 886 patients enrolled, 163 were assigned to TCZ 8 mg/kg monotherapy. The remaining 723 patients were assigned to combination therapy, with 363 randomized to receive a starting dose of TCZ 4 mg/kg plus DMARDs and 360 to receive a starting dose of TCZ 8 mg/kg plus DMARDs. In the initial TCZ 4 mg/kg plus DMARDs group, 152 patients (41.9%) at week 8 and 68 patients (18.7%) after 8 week escalated to TCZ 8 mg/kg plus DMARDs. Overall, the 24-week study was completed by 82.5% of patients. By week 24, 49.7%, 27.1%, and 10.3% of the patients in the 8 mg/kg TCZ plus DMARDs group and 47.9%, 24.5%, and 7.4% of the patients in the 8 mg/kg TCZ monotherapy group had attained ACR20/50/70 responses. The safety profiles and efficacy were similar for the TCZ monotherapy and the TCZ plus DMARD groups. Therefore, the efficacy of TCZ monotherapy and combination therapy with MTX or DMARDs was similar, demonstrating that TCZ monotherapy can

provide patients who cannot use MTX with a good quality of life (QoL).

In addition, TCZ showed a good continuation rate and could induce drug-free remission. Reduced efficacy is one of the issues when using a treatment for RA that includes biologics. In the Danish DANBIO registry, the drug adherence rate after 48 months was 64%.[62] In another multicentre registry, the Japanese REAL, the continuation rate for TCZ at 2.5 years was 67%.[63] The DREAM study reported findings on the maintenance of TCZ-free remission in TCZ monotherapy;[64] remisson rates following the cessation of TCZ were 35.1% and 13.4% at 24 and 52 weeks, respectively. Even if recurrence was noted after TCZ cessation, TCZ re-administration could re-induce remission.[65] The OPTION trial reported on maintenance of TCZ-free remission for combination therapy with MTX; efficacy after the cessation of TCZ was 52.5% at 12 months.[66] Relapses occurred in 47.5% patients, half of which were noted during the first 3 months after the final TCZ administration.

The systemic effects of TCZ enhance the satisfaction of RA patients; health-related QoL (HRQoL) was reportedly improved with TCZ therapy.[67,68] Depression, fatigue, and quality of sleep in patients treated with TCZ also improved.[69–71]

The safety profile of TCZ monotherapy was first published in 2010.[72] The overall incidence of adverse events (AE) and serious AE (SAE) rates were 465.1/100 patient-year (PY) and 6.22/100 PY, respectively. As for the risk of AEs for RA patients treated with TCZ, pooled odds ratios (ORs) indicate a statistically significantly increased risk of AEs (OR = 1.53; 95% confidence interval (CI) = 1.26–1.86) in addition to a heightened risk of infection (OR = 1.30; 95% CI = 1.07–1.58). The safety profile of TCZ combination therapy was first published in 2011.[73] Overall AE and SAE rates were 278.2/100 PY and 14.4/100 PY, respectively. These events included serious infections (4.7/100 PY), opportunistic infections (0.23/100 PY), and gastrointestinal perforations (0.28/100 PY). Pooled ORs revealed a significantly increased risk of AEs (OR = 1.53; 95% CI = 1.26–1.86) and infection (OR = 1.30; 95% CI = 1.07 = 1.58) for patients treated with 8 mg/kg TCZ plus MTX compared with that for controls.

TCZ blocks IL-6 function and has been shown to have excellent efficacy and tolerability when used in the treatment of RA. The efficacy of TCZ monotherapy appears to be similar to that of combination therapy with DMARDs or MTX. In addition, the recent development of the option of subcutaneous administration of TCZ may also be beneficial for patients with RA. Because of the outstanding efficacy of TCZ, other new biological agents that target IL-6 are also being developed. These IL-6 inhibitors can be expected to constitute a new class of antirheumatic drugs in the future.

The clinical efficacy of TCZ in RA is mediated by the inhibition of IL-6-induced RANKL induction followed by osteoclastogenesis and suppression of IL-6-induced production of matrix metalloproteinases.[74] Moreover, it has been shown that TCZ corrects Th17 ($CD4^+IL\text{-}17^+$)/Treg ($CD4^+CD25^{high}Foxp3^+$) imbalance in RA patients.[75] Other studies have found both that TCZ induced a significant reduction in the peripheral pre-switch and post-switch memory B cells of RA patients[76] and that TCZ but not TNF inhibitors significantly reduced somatic hypermutation in immunoglobulin gene rearrangements in pre-switch memory B cells.[77] These findings thus indicate that modulation of memory B cells may constitute a potential target for TCZ.

Additional Applications of Tocilizumab for Other Immune-Mediated Diseases

In addition to the diseases for which it has been approved, IL-6 blockade strategy is expected to come into extensive use for the treatment of various other immune-mediated diseases; several clinical studies to evaluate the efficacy and safety of TCZ for such diesases are in progress.

Systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease, characterized by skin and tissue fibrosis, vasculopathy, and immune abnormalities.[78] Numerous studies have analyzed the pathogenic mechanisms of SSc, but no effective treatment has been established yet.[79] IL-6 is a potential target for SSc therapy for several reasons.[80,81] IL-6 levels in the sera of SSc patients are elevated and these levels correlate well with skin severity scores.[82–86] Indeed, the culture supernatants of peripheral blood mononuclear cells and skin tissues from patients with SSc were found to contain

higher concentrations of IL-6 than did those from controls.[87–89] Furthermore, in vitro studies indicate that IL-6 may contribute to fibrosis by inducing collagen production[27] by dermal fibroblasts and induce their differentiation into myofibroblasts.[90] Moreover, anti-IL-6 Ab suppressed procollagen type 1 production in vitro in fibroblasts derived from SSc patients.[91] Another reason for targeting IL-6 in SSc is that SSc serum mediated largely by IL-6 was found to induce endothelial cell activation and apoptosis in endothelial cell-neutrophil co-cultures.[92] Loss of IL-6 expression led to amelioration of skin and lung fibrosis in a mouse model immunized with DNA topoisomerase 1 and Freund's complete adjuvant.[93] Meanwhile, IL-6 deficiency produced by either administration of anti-IL-6R Ab or gene knockout in a bleomycin-induced mouse model of SSc suppressed fibroblast activation, which resulted in a reduction of dermal thickness and hardness.[94]

We reported our clinical findings for two patients with SSc who responded well to TCZ.[95] The skin became softer as indicated by the modified Rodnan total skin score and a novel device known as Vesmeter, which can measure viscosity, elasticity, and hardness of the skin.[96] Histological analysis showed that collagen fibre bundles had become thinner and activated myofibroblasts reduced in the dermis after a 6-month treatment with TCZ.[94,95] These findings indicate that IL-6 blockade strategy is a promising approach for the treatment of SSc. A phase II/III, multicenter, randomized, double-blind, placebo-controlled study is in progress to assess the efficacy and safety of TCZ as compared with a placebo for patients with SSc.

Polymyositis

Inflammatory myopathies encompass a group of acquired muscle disorders that includes polymyositis (PM), dermatomyositis, and inclusion body myositis; these disorders share the clinical features of progressive symmetrical muscle weakness and mononuclear inflammatory cell infiltrating muscle tissue.[97] PM appears to be another suitable target disease for TCZ for three reasons. Firstly, excessive IL-6 expression has been found in the sera and in the infiltrating mononuclear cells in the muscles of PM patients.[98–101] Secondly, infiltrating cytotoxic T cells are thought to be involved in muscle fiber damage and IL-6 reportedly functions as a helper factor in the induction of cytotoxic T cells.[19] Thirdly, in a model of myosin-induced experimental myositis it was shown that control mice developed clinically manifest muscle damage, whereas IL-6-deficient mice showed no clinical or histological signs of muscle damage.[102] In another model of PM, known as C protein-induced myositis, intraperitoneal administration of anti-IL-6R Ab reduced the severity of myositis.[103]

We therefore administered TCZ to two PM patients who had been refractory to corticosteroids and immunosuppressive drugs for more than 5 years. Creatine phosphokinase levels of both patients normalized and magnetic resonance images showed that high-intensity zones in the thigh muscles had disppeared,[104] indicating that TCZ administration may also be an option for the treatment of refractory PM.

Vasculitis syndrome and polymyalgia rheumatica

Vasculitis syndrome refers to a heterogeneous group of disorders featuring inflammation and damage of blood vessel walls, leading to tissue necrosis.[105,106] According to the 2012 revised international Chapel Hill Consensus Conference nomenclature of primary vasculitis syndrome, large vessel vasculitis includes giant cell arteritis (GCA) and Takayasu arteritis (TA), medium vessel vasculitis comprises polyarteritis nodosa and Kawasaki disease, and small vessel vasculitis includes anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, immune complex small vessel vasculitis, and hypocomplementary urticarial vasculitis. The pathological significance of IL-6 for large vessel vasculitis has been well documented.[107,108] It was found that the serum concentrations of IL-6 were elevated at the onset and during clinical relapse and correlated with the disease activity of GCA and TA,[109–115] while tissue-infiltrating cells reportedly produced major quantities of IL-6 in patients with GCA and TA.[116–119]

Nishimoto et al were the first to report that TCZ treatment for a 20 year old woman with refractory active TA improved clinical manifestations and abnormal laboratory findings.[120] It was subsequently reported that TCZ treatment induced a rapid remission in five patients with GCA and two patients with TA, so that cumulative corticosteroid doses could be reduced substantially.[121] Corticosteroid treatment is currently recognized as the mainstay therapy for GCA, but interestingly, TCZ as

monotherapy without corticosteroids was effective for two of the patients with GCA in the study. Furthermore, recent case reports and case series of off-label use of TCZ have demonstrated its outstanding efficacy for refractory GCA and TA.[122–132] It has been reported to date that the treatment had rapid beneficial effects on 22 patients with GCA and 12 patients with TA, resulting in the successful tapering of corticosteroids, with the exception of one GCA patient. Instrumental examination of the arteries involved by determining the vascular ^{18}F-fluorodeoxyglucose (FDG) uptake on positron emission tomography by means of CT and ultrasonographic resolution, showed improvement in all cases evaluated. These results strongly suggest that IL-6 inhibition may become a novel therapeutic strategy for large vessel vasculitis. As of this study, a phase II, randomized, double-blind, placebo controlled study of TCZ for patients with GCA has just been initiated.

In addition to the clinical effect of TCZ on large vessel vasculitis, the treatment reportedly improved clinical symptoms in a patient with a chimeric anti-CD20 antibody rituximab-refractory cryoglobulinemic vasculitis.[133] A patient with myeloperoxidase-ANCA-associated crescentic glomerulonephritis complicated by RA also showed improvements.[134]

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder that affects the elderly and is characterized by aching and morning stiffness in the shoulders, neck, and pelvic girdles.[107] PMR can occur in its isolated form or may be associated with GCA. Although the pathogenesis of this disorder remains unknown, IL-6 has been identified as the only cytokine occurring at a consistently high level in patients with the active form of the disease; it is recognized as the most sensitive indicator of disease activity and course.[107,109–111,135] IL-6 was also reported to be elevated in the synovial fluid[136] and in the muscle interstitial concentrations of cytokines.[137] IL-6 inhibition with TCZ may thus constitute a novel strategy for the treatment of PMR. Low doses (15–20 mg/day) of corticosteroids are effective for PMR, but 43%–65% of patients with this disease reportedly experienced at least one steroid-related adverse event such as osteoporosis, fragility fracture, or arterial hypertension.[138,139]

We found that TCZ had a significantly beneficial effect on a patient with long-standing steroid-refractory PMR complicated by diabetes, osteoporosis, and hypertension.[140] After five injections of TCZ, all symptoms such as pain and morning stiffness improved and the patient was judged to be in remission; improvements were such that the prednisolone dose could be reduced. In addition, TCZ treatment was found to produce a disease-free status for four patients with PMR complicated with GCA.[121] As mentioned before, two patients with PMR treated with TCZ but not with corticosteroids also attained remission. Moreover, recent studies have demonstrated the ameliorative and steroid-sparing effects of TCZ for patients with PMR,[126,130] while a phase IIa clinical trial of tocilizumab for the treatment of polymyalgia rheumatica is in progress.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology that mainly affects young women.[141] While pathogenesis of SLE remains unclear, cytokine dysregulation is pervasive in SLE and its expression profiles may serve as a marker of disease activity and severity. Recent findings have highlighted the presence of the type I interferon pathway[142] or the activation of Th17 cell[143] in the pathogenesis of SLE. IL-6 has also been shown to play a role in the development of SLE,[144] since it was found that serum IL-6 levels of SLE patients were elevated,[145–147] urinary excretion of IL-6 had increased in SLE patients with active proliferating lupus nephritis,[146,148] and IL-6 levels were elevated in the cerebrospinal fluid of SLE patients with central nervous system (CNS) involvement.[149] A comparison with healthy controls showed that SLE patients have significantly more IL-6 secreting peripheral blood mononuclear cells.[150] Moreover, lymphoblastoid cells isolated from SLE patients produced higher levels of IL-6 and blocking of IL-6 inhibited anti-double-stranded DNA (dsDNA) production in vitro.[151,152] In murine SLE models, IL-6 administration exacerbated glomerulonephritis,[153,154] while IL-6 blockade by means of anti-IL-6R or anti-IL-6 Ab prevented the onset and progression of the disease.[155,156] Mice with epidermal loss of JunB reportedly developed an SLE phenotype associated with enhanced epidermal IL-6 secretion.[157] Facial skin biopsies of SLE patients displayed low levels of JunB protein expression and high levels of IL-6 and activated STAT3 within lupus lesions.[157]

An open-label phase I dosage-escalation study (2 mg/kg, 4 mg/kg or 8 mg/kg of TCZ, every 2 weeks for 12 weeks) with an enrollment of 16 SLE patients with mild-to-moderate disease activity showed significant improvement in disease activity in 8 of the 15 evaluable patients, with a median reduction of 47% in levels of anti-dsDNA antibodies.[158] The percentage of $CD38^{high}CD19^{low}IgD^{negative}$ plasma cells in the peripheral blood, which was higher for SLE patients than for normal controls (mean 5.3% vs. 1.2%), had been significantly reduced to 3.1% after 6 weeks. Moreover, according to two case reports, TCZ was efficacious for a patient with intractable SLE complicated by RA and treated in combination with tacrolimus.[159] TCZ was also efficacious for a multiple drug-refractory SLE patient with cutaneous lupus and urticarial vasculitis.[160] These results indicate that TCZ represents a promising therapeutic biologic for SLE.

Relapsing polychondritis

Relapsing polychondritis is a very rare disease, characterized by recurrent inflammation and cartilage destruction;[161,162] the cartilaginous structures of ear, nose, joints and respiratory tract are especially affected.[163] Autoimmune reactions to antigens present in cartilage, for example, type II, IX and XI collagen and matrilin and excess generation of proinflammatory cytokines and chemokines, are thought to evoke the disease symptoms.[164] The involvement of laryngotracheal cartilage causes severe airway destruction and thus requires vigorous treatments with corticosteroids and immunosuppressive drugs. Biologics including TNF inhibitors, rituximab, and IL-1R antagonist anakinra, have been successfully used for refractory relapsing polychondritis.[165] Two patients with relapsing polychondritis, who had been refractory to conventional regimens, were treated with TCZ.[166] The treatment ameliorated clinical symptoms related to the upper and lower airways. In one patient, airway narrowing of the bronchi was improved within one year of treatment while in the other patient Gallium citrate uptake in the involved cartilages had disappeared 21 months after the treatment. The TCZ treatment for these two patients has continued for more than five years without any signs of relapse so that the prednisolone dose could be reduced. Moreover, in a patient with relapsing polychondritis, tocilizumab caused a complete resolution of all clinical symptoms, which had been refractory to conventional therapy and adalimumab, a TNF inhibitor.[167] Because of the very rare occurrence of the disease it is difficult to perform a randomized controlled trial and in order to evaluate its efficacy for this disorder there is therefore an urgent need for reports on clinical experience with the use of TCZ for relapsing polychndritis.

Neuromyelitis optica

Neuromyelitis optica (NMO) is a chronic inflammatory CNS disorder predominantly affecting the spinal cord and optic nerves, in which anti-aquaporin-4 (AQP4) autoantibodies perform a pathologic function.[168,169] AQP4, which belongs to the aquaporin family of integral membrane proteins that conduct water through the cell membrane, is constitutively expressed in astrocytes and is upregulated in response to direct insult to the CNS.[170] Several studies have reported a marked increase of IL-6 in cerebrospinal fluid of patients with NMO.[171–174] Moreover, it has been found that the population of plasmablasts showing the $CD19^{int}CD27^{high}CD38^{high}CD180^{negative}$ phenotype was selectively increased in the peripheral blood of NMO patients and that anti-AQP4 Abs were mainly produced by the plasmablasts.[175] IL-6 enhanced the survival of plasmablasts, as well as anti-AQP4 Ab secretion, whereas anti-IL-6R Ab diminished their survival and, indeed, clinical improvement and reduced serum levels of anti-AQP4 Abs were observed in a patient with NMO following therapy with TCZ.[176] Moreover, the prominent positive effect of TCZ was reported in a patient with NMO who had failed to respond to numerous immunosuppressive interventions, including high-dose corticosteroids, mitoxantrone, plasma exchange, rituximab and anti-CD52 Ab, alemtuzumab.[177]

Crohn's disease

Crohn's disease (CD) is a chronic inflammatory bowel disease of unknown etiology. However, both Th1 and Th17 cells are believed to play a central role in its development.[178,179] IL-6 also contributes to its development, since elevated levels of IL-6 have been detected in the blood and in the cultures of colonic mucosal specimens from CD patients.[180–182] In a colitis mouse model generated by transfer of $CD45RB^{high}CD4^{positive}$ T cells into SCID mice, anti-IL-6R Ab prevented the occurrence of signs and symptoms of colitis.[183]

A randomized pilot trial of TCZ for 36 patients with active CD demonstrated that 80% of the patients given 8 mg/kg every 2 weeks showed a clinical response, as compared with only 31% of placebo-injected patients.[184] Colitis-associated intestinal perforation is one of the most serious complications of inflammatory bowel diseases, but there was no event of gastrointestinal perforation in TCZ- or placebo-injected patients in the clinical trial for CD.

Adult-onset still's disease

Adult-onset Still's disease (AOSD) is a chronic inflammatory disease characterized by four cardinal symptoms, namely spiking fever, evanescent maculopapular rash, arthritis, and leukocytosis.[185,186] Pathologically it resembles systemic JIA; IL-6 levels are elevated and correlate with disease activity in patients with AOSD.[187–190] Although the efficacy and safety of TCZ for AOSD have not yet been evaluated in a randomized controlled trial, numerous case and pilot studies have shown that TCZ treatment improved clinical symptoms and signs of AOSD in patients who had been refractory to conventional treatment regimens and biologics, including TNF inhibitors and anakinra.[191–207] These findings indicate that TCZ may become a first-line biologic for the treatment of AOSD.

Amyloid A amyloidosis

Amyloid A amyloidosis is a serious complication of chronic inflammatory diseases in which amyloid fibril deposition causes progressive deterioration in various organs.[208] SAA, an acute phase protein produced in the liver, is an amyloid fibril precursor protein and sustained high concentrations of SAA have been found to correlate with progression of renal amyloid diseases.[209] Several therapeutic strategies have been proposed for the treatment of amyloid A amyloidosis, but the inhibition of SAA appears to be the most suitable approach, since long-term suppression of its level (less than 10 mg/L) was found to lead to a regression or stabilization of the amyloid load.[210] Activation of the SAA1 gene depends primarily on IL-6,[211,212] and indeed, TCZ administration was found to cause a marked reduction of serum SAA concentrations, irrespective of the underlying diseases.[53,213–215] Case studies of amyloid A amyloidosis complicated with RA, JIA, or latent tuberculosis reported that TCZ had an ameliorative clinical effect on gastrointestinal symptoms and renal function.[216–222] Surprisingly, amyloid A fibril deposits were found to have disappeared in two cases after only three injections of TCZ.[217,219] This suggests that IL-6 blocking may be an innovative strategy for amyloid A amyloidosis complicated with chronic inflammatory diseases.[223]

Behcet's disease and uveitis

Behcet's disease (BD) is a systemic inflammatory disease of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, and other manifestations that include neurological, gastrointestinal, and vascular involvement.[224] The involvement of IL-6 has been demonstrated in the pathological development of BD.[225–228] We administered TCZ in the treatment of one BD patient with posterior uveitis who had been suffering from BD for 10 years and had been treated with colchicine, prednisolone, and ciclosporin.[229] Treatment with infliximab used for recurrent posterior uveitis brought the uveitis attacks under satisfactory control. When a severe relapse of posterior uveitis occurred 16 months later, however, TCZ was initiated and continuous treatment for 1 year reduced the number of ocular attacks and the BD Current Activity Form score.[229] IL-6 may well be the most important inflammatory cytokine involved in both acute and chronic progressive neuro-BD,[230–232] and a case report of off-label use with TCZ noted outstanding and beneficial effects in a patient with neuro-BD refractory to all previous treatment regimens.[233]

Autoimmune and inflammatory uveitis refers to a group of potentially blinding intraocular inflammatory diseases that arise without a known infectious trigger and which are often associated with immunological responses to unique proteins; they are also known to frequently occur in conjunction with systemic diseases.[234] IL-6 is known to be elevated in the vitreous body of patients with active intermediate and posterior uveitis,[235–239] and both Th1 and Th17 cells have been found to play a pathologic role in experimental autoimmune uveoretinitis, an animal model of uveitis.[240] Blockade of IL-6 signaling reportedly suppresses autoimmune uveoretinitis and its protective effect is mediated by Treg induction and by Th17 and Th1 inhibition.[240–242] This indicates that TCZ may constitute a therapeutic option for uveitis; a recent

case report on the clinical efficacy of TCZ for two patients with anti-TNFα refractory uveitis has suggested this possibility.[243] In this context, an open-label trial has just been started to assess the efficacy and safety of TCZ in the management of JIA-associated vision-threatening uveitis refractory to other modes of systemic immunosuppression.

Other candidate diseases

Case series or reports of off-label use of TCZ have also raised the possibility that TCZ might be applicable for the treatment of other diseases. These include graft-versus-host disease,[244,245] acquired hemophilia A,[246] autoimmune hemolytic anemia,[247–249] remitting seronegative, symmetrical synovitis with pitting edema,[250] pulmonary arterial hypertension,[251–253] tumor necrosis factor receptor-associated periodic syndrome,[254] atopic dermatitis,[255] interstitial granulomatous dermatitis,[256] and sciatica.[257] Moreover, some studies have reported the efficacy of TCZ for spondyloarthritides such as ankylosing spondylitis[258–262] and reactive arthritis.[263,264] However, recent clinical trials of TCZ[49] and sarilumab,[265] a fully human anti-IL-6R Ab, could not detect any favorable effect on ankylosing spondylitis, nor did our study of the clinical effect of TCZ on skin and joint lesions in two patients with psoriasis.[48] Observational studies of RA patients complicated with type 2 diabetes mellitus treated with TCZ found a reduction in hemoglobin A1c (HbA1c) levels.[266] Moreover, a study of 11 non-diabetic patients with RA detected, after 3 months of tocilizumab treatment, a significant decrease in insulin resistance indexes such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the leptin-to-adiponectin ratio.[267] Serum levels of reactive oxygen metabolites also decreased in RA patients treated with TCZ.[268] It can thus be expected that long-term TCZ treatment may offer protection against the progression of atherosclerosis leading to cardiovascular events.[269] A randomized, open-label, parallel-group, multicenter study is in progress to determine and assess the rate of cardiovascular events for patients with RA following treatment with TCZ, with a comparison to treatment with etanercept, a TNF inhibitor, as a control.

Conclusions and Future Prospects

Currently TCZ is approved worldwide for the treatment of RA, Additionally, in several countries it is approved for treatment of Castleman's disease and systemic and polyarticular JIA. In view of the favorable results for off-label use of TCZ and the pathologic role of IL-6 in various immune-mediated diseases, TCZ is expected to be widely used in the treatment of such diseases. However, further clinical trials are required to achieve this goal.

The mechanisms through which TCZ exerts its therapeutic effects on various phenotypically different diseases are not yet well understood. It is possible that TCZ can rectify the imbalance of Th17/Treg in various diseases,[18] as seen in treatment of RA.[75] On the other hand, TCZ could exert its beneficial clinical effect by inhibiting pathological autoantibody production, since TCZ treatment was found to lead to a reduction in the pathologic $CD38^{high}CD19^{low}IgD^{negative}$ plasma cells of SLE patients[158] and to diminish the survival of plasmablasts—that is, $CD19^{int}CD180^{negative}CD27^{+}CD38^{+}$ cells, which produce the anti-AQP4 Ab seen in NMO.[175,176]

Finally, as already mentioned, IL-6 synthesis is regulated by transcriptional levels and post-transcriptional mechanisms. It has already been shown that some viral products derived from Kaposi's sarcoma-associated herpes virus, human T lymphotropic virus-1, human immunodeficiency virus-1, or human hepatitis virus B, could constitutively activate transcriptional activation of the IL-6 gene and/or inhibit its mRNA degradation.[270–276] For these reasons, clarification of the cell source and the mechanism of dysregulated persistent IL-6 production is expected to aid and facilitate the investigation of the pathogenesis of a wide range of diseases.

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As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

References

1. Kishimoto T. Interleukin-6: from basic sciences to medicine-40 years in immunology. *Annu Rev Immunol.* 2005;23:1–21.
2. Zilberstein A, Ruggieri R, Korn JH, Revel M. Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines. *EMBO J.* 1986;5:2529–37.
3. Hirano T, Yasukawa K, Harada H, et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature.* 1986;324:73–6.
4. Somers W, Stahl M, Seehra JS. 1.9 A crystal structure of interleukin 6: implications for a novel mode of receptor dimerization and signaling. *EMBO J.* 1997;16:989–97.
5. Hirano T, Taga T, Yasukawa K, et al. Human B-cell differentiation factor defined by an anti-peptide antibody and its possible role in autoantibody production. *Proc Natl Acad Sci U S A.* 1987;84:228–31.
6. Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood.* 1989;74:1360–7.
7. Kopf M, Baumann H, Freer G, et al. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature.* 1994;368:339–42.
8. Suematsu S, Matsuda T, Aozasa K, et al. IgG1 plasmacytosis in interleukin 6 transgenic mice. *Proc Natl Acad Sci U S A.* 1989;86:7547–51.
9. Ohzato H, Yoshizaki K, Nishimoto N, et al. Interleukin-6 as a new indicator of inflammatory status: detection of serum levels of interleukin-6 and C-reactive protein after surgery. *Surgery.* 1992;111:201–9.
10. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol.* 2004;4:499–511.
11. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J.* 1990;265:621–36.
12. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest.* 2004;113:1271–6.
13. Liuzzi JP, Lichten LA, Rivera S, et al. Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. *Proc Natl Acad Sci U S A.* 2005;102:6843–8.
14. Asano S, Okano A, Ozawa K, et al. In vivo effects of recombinant human interleukin-6 in primates: stimulated production of platelets. *Blood.* 1990;75:1602–5.
15. Hurst SM, Wilkinson TS, McLoughlin RM, et al. IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. *Immunity.* 2001;14:705–14.
16. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature.* 2006;441:235–8.
17. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. *Annu Rev Immunol.* 2009;27:485–517.
18. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol.* 2010;40:1830–35.
19. Okada M, Kitahara M, Kishimoto S, Matsuda T, Hirano T, Kishimoto T. IL-6/BSF-2 functions as a killer helper factor in the in vitro induction of cytotoxic T cells. *J Immunol.* 1988;141:1543–9.
20. Hirano T, Taga T, Nakano N, et al. Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2). *Proc Natl Acad Sci U S A.* 1985;82:5490–4.
21. Kotake S, Sato K, Kim KJ, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J Bone Miner Res.* 1996;11:88–95.
22. Palmqvist P, Persson E, Conaway HH, Lerner UH. IL-6, leukemia inhibitory factor, and oncostatin M stimulate bone resorption and regulate the expression of receptor activator of NF-kappa B ligand, osteoprotegerin, and receptor activation of NF-kappa B in mouse calvariae. *J Immunol.* 2002;169:3353–62.
23. Jilka RL, Hangoc G, Girasole G, et al. Increased osteoclast development after estrogen loss: mediation by interleukin-6. *Science.* 1992;257:88–91.
24. Islander U, Jochems C, Lagerquist MK, Forsblad-d'Elia H, Carlsten H. Estrogens in rheumatoid arthritis; the immune system and bone. *Mol Cell Endocrinol.* 2011;335:14–29.
25. Nakahara H, Song J, Sugimoto M, et al. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. *Arthritis Rheum.* 2003;48:1521–9.
26. Grossman RM, Krueger J, Yourish D, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. *Proc Natl Acad Sci U S A.* 1989;86:6367–71.
27. Duncan MR, Berman B. Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. *J Investig Dermatol.* 1991;97:686–92.
28. Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood.* 1995;86:1243–54.
29. Taga T, Hibi M, Hirata Y, et al. Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130. *Cell.* 1989;58:573–81.
30. Narazaki M, Yasukawa K, Saito T, et al. Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130. *Blood.* 1993;82:1120–6.
31. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC. Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science.* 2003;300:2101–4.
32. Kishimoto T, Akira S, Taga T. Interleukin-6 and its receptor: a paradigm for cytokines. *Science.* 1992;258:593–7.
33. Garbers C, Hermanns HM, Schaper F, et al. Plasticity and cross-talk of interleukin 6-type cytokines. *Cytokine Growth Factor Rev.* 2012;23:85–97.

34. Aoki Y, Narazaki M, Kishimoto T, Tosato G. Receptor engagement by viral interleukin-6 encoded by Kaposi sarcoma-associated herpes virus. *Blood.* 2001;98:3042–9.
35. Akira S, Kishimoto T. IL-6 and NF-IL6 in acute-phase response and viral infection. *Immunol Rev.* 1992;127:25–50.
36. Matsusaka T, Fujikawa K, Nishio Y, et al. Transcription factors NF-IL6 and NF-kappa B synergistically activate transcription of the inflammatory cytokines, interleukin 6 and interleukin 8. *Proc Natl Acad Sci U S A.* 1993;90:10193–7.
37. Matsushita K, Takeuchi O, Standley DM, et al. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. *Nature.* 2009;458:1185–90.
38. Iwasaki H, Takeuchi O, Teraguchi S, et al. The IkB kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. *Nat Immunol.* 2011;12: 1167–75.
39. Tanaka T, Narazaki M, Kishimoto T. Therapeutic targeting of the interleukin-6 receptor. *Annu Rev Pharmacol Toxicol.* 2012;52:199–219.
40. Sato K, Tsuchiya M, Saldanha J, et al. Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth. *Cancer Res.* 1993;53: 851–6.
41. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood.* 2008;112:3959–64.
42. Tanaka T, Ogata A, Narazaki M. Tocilizumab for the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol.* 2010;6:843–54.
43. Jones G, Ding C. Tocilizumab: a review of its safety and efficacy in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord.* 2010;3: 81–9.
44. Yokota S, Tanaka T, Kishimoto T. Efficacy, safety and tolerability of tocilizumab in patients with systemic juvenile idiopathic arthritis. *Ther Adv Musculoskelet Dis.* 2012;4:387–97.
45. Alonzi T, Fattori E, Lazzaro D, et al. Interleukin 6 is required for the development of collagen-induced arthritis. *J Exp Med.* 1998;187:461–8.
46. Kagari T, Doi H, Shimozato T. The importance of IL-1 beta and TNF-alpha, and the noninvolvement of IL-6, in the development of monoclonal antibody-induced arthritis. *J Immunol.* 2002;169:1459–66.
47. Iwakura Y, Nakae S, Saijo S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. *Immunol Rev.* 2008;226:57–79.
48. Ogata A, Umegaki N, Katayama I, Kumanogoh A, Tanaka T. Psoriatic arthritis in two patients with an inadequate response to treatment with tocilizumab. *Joint Bone Spine.* 2012;79:85–7.
49. Sieper J, Porter-Brown B, Thompson L, Harari O, Dougados M. Tocilizumab (TCZ) is not effective for the treatment of ankylosing spondylitis (AS): result of phase 2, international multicentre randomized double-blind placebo-controlled trial. *Ann Rheum Dis.* 2012;71(Suppl 3):110.
50. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis.* 2010;69:88–96.
51. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomized controlled trial of tocilizumab. *Ann Rheum Dis.* 2007;66: 1162–7.
52. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol.* 2009;19:12–9.
53. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al; OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet.* 2008;371:987–97.
54. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate: results from a substudy of the multicenter double-blind, placebo controlled trial of tocilizumab in inadequate responders to methotrexate alone. *Arthritis Rheum.* 2010;62:33–43.
55. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 2008;58:2968–80.
56. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis.* 2008;67:1516–23.
57. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum.* 2011;63:609–21.
58. Smolen JS, Avila JC, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: dissociation of the link between inflammation and destruction. *Ann Rheum Dis.* 2012;71:687–93.
59. Dougados M, Kissel K, Sheeran T, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomized controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis.* 2013;72: 43–50.
60. Bykerk VP, Ostör AJ, Alvaro-Gracia J, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis.* 2012;71:1950–4.
61. Weinblatt ME, Kremer J, Cush J, et al. Tocilizumab as monotherapy or in combination with nonbiologic DMARDs: 24-week results of an open-label, clinical practice study (ACT-STAR). *Arthritis Care Res (Hoboken).* Sep 12, 2012. [Epub ahead of print.]
62. Hetland ML, Christensen IJ, Tarp U, et al. All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum.* 2010;62:22–32.
63. Sakai R, Tanaka M, Nanki T, et al. for the REAL Study Group. Drug retention rates and relevant risk factors for drug discontinuation due to adverse events in rheumatoid arthritis patients receiving anticytokine therapy with different target molecules. *Ann Rheum Dis.* 2012;71:1820–6.
64. Nishimoto N. Japanese MRA study group for RA. Drug free remission after cessation of actemra monotherapy (DREAM Study). *Ann Rheum Dis.* 2010;69(Suppl 3):98.
65. Nishimoto N. Japanese MRA study group for RA. Retreatment efficacy and safety to tocilizumab in patients with rheumatoid arthritis at recurrence (RESTORE study). *Ann Rheum Dis.* 2010;69(Suppl 3):537.
66. Aguilar-Lozano L, Padilla-Ibarra J, Sandoval-Castro C, et al. The length of remission and rate of relapse after tocilizumab withdrawal in rheumatoid arthritis patients. *Ann Rheum Dis.* 2012;71(Suppl 3):69.
67. Fusama M, Nakahara H, Hamano Y, et al. Improvement of health status evaluated by Arthritis Impact Measurement Scale 2 (AIMS-2) and Short Form-36 (SF-36) in patients with rheumatoid arthritis treated with tocilizumab. *Mod Rheumatol.* Jun 6, 2012. [Epub ahead of print.]
68. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology (Oxford).* 2012;51:1860–9.
69. Miwa Y, Furuya H, Yanai R, et al. Comparison of efficacy of four biological agents for rheumatoid arthritis patients using the HRQoL questionnaire and depression scale. *Ann Rheum Dis.* 2012;71(Suppl 3):663.

70. Foti R, Russo R, Malavolta N, et al. Effects of tocilizumab in combination with non biologic DMARDs on early improvement of anemia and fatigue in adult patients with moderate to severe active rheumatoid arthritis. *Ann Rheum Dis*. 2012;71(Suppl 3):671.
71. Fragiadaki K, Tektonidou MG, Konsta M, Chrousos GP, Sfikakis PP. Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. *J Rheumatol*. 2012;39:60–2.
72. Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. *Mod Rheumatol*. 2010;20:222–32.
73. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther*. 2011;13:R141.
74. Hashizume M, Mihara M. The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis*. 2011:Article ID 765624.
75. Samson M, Audia S, Janikashvili N, et al. Brief report: inhibition of interleukin-6 function corrects Th17/Treg cell imbalance in patients with rheumatoid arthritis. *Arthritis Rheum*. 2012;64:2499–503.
76. Roll P, Muhammad K, Schumann M, et al. In vivo effects of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment. *Arthritis Rheum*. 2011;63:1255–64.
77. Muhammad K, Roll P, Seibold T, et al. Impact of IL-6 receptor inhibition on human memory B cells in vivo: impaired somatic hypermutation in pre-switch memory B cells and mutational targeting in memory B cells. *Ann Rheum Dis*. 2011;70:1507–10.
78. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360:1989–2003.
79. Hasegawa M, Takehara K. Potential immunologic targets for treating fibrosis in systemic sclerosis: a review focused on leukocytes and cytokines. *Semin Arthritis Rheum*. 2012;42:281–96.
80. Barnes TC, Anderson ME, Moots RJ. The many faces of interleukin-6: the role of IL-6 in inflammation, vasculopathy, and fibrosis in systemic sclerosis. *Int J Rheumatol*. 2011:721608.
81. O'Reilly S, Ciechomska M, Cant R, Hugle T, van Larr JM. Interleukin-6, its role in fibrosing conditions. *Cytokine Growth Factor Rev*. 2012;23:99–107.
82. Hasegawa M, Sato S, Fujimoto M, Ihn H, Kikuchi K, Takehara K. Serum levels of interleukin 6 (IL-6), oncostatin M, soluble IL-6 receptor, and soluble gp130 in patients with systemic sclerosis. *J Rheumatol*. 1998;25:308–13.
83. Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. *J Dermatol Sci*. 2001;27:140–6.
84. Gourh P, Arnett FC, Assassi S, et al. Plasma cytokine profiles in systemic sclerosis: associations with autoantibody subsets and clinical manifestation. *Arthritis Res Ther*. 2009;11:R147.
85. Radstake TR, van Bon L, Broen J, et al. The pronounced Th17 profiles in systemic sclerosis (SSc) together with intracellular expression of TGFbeta and IFNgamma distinguishes SSc phenotype. *Plos One*. 2009;4:e5903.
86. Khan K, Xu S, Nihtyanova S, et al. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. *Ann Rheum Dis*. 2012;71:1235–42.
87. Feghali CA, Bost KL, Boulware DW, Levy LS. Mechanisms of pathogenesis in scleroderma. I. Overproduction of interleukin 6 by fibroblasts cultured from affected skin sites of patients with scleroderma. *J Rheumatol*. 1992;19:1207–11.
88. Koch AE, Kronfeld-Harrington LB, Szekanecz Z, et al. In situ expression of cytokines and cellular adhesion molecules in the skin of patients with systemic sclerosis: their role in early and late disease. *Pathobiology*. 1993;61:239–46.
89. Gurram M, Pahwa S, Frieri M. Augmented interleukin-6 secretion in collagen-stimulated peripheral blood mononuclear cells from patients with systemic sclerosis. *Ann Allergy*. 1994;73:493–6.
90. Gallucci RM, Lee EG, Tomasek JJ. IL-6 modulates alpha-smooth muscle actin expression in dermal fibroblasts from IL-6-deficient mice. *J Invest Dermatol*. 2006;126:561–8.
91. Kawaguchi Y, Hara M, Wright TM. Endogenous IL-1alpha from systemic sclerosis fibroblasts induces IL-6 and PDGF-A. *J Clin Invest*. 1999;102:1253–60.
92. Barnes TC, Spiller DG, Anderson ME, Edwards SW, Moots RJ. Endothelial activation and apoptosis mediated by neutrophil-dependent interleukin 6 trans-signalling: a novel target for systemic sclerosis? *Ann Rheum Dis*. 2011;70:368–72.
93. Yoshizaki A, Yanaba K, Ogawa A, Asano Y, Kadono T, Sato S. Immunization with DNA topoisomerase I and Freund's complete adjuvant induces skin and lung fibrosis and autoimmunity via interleukin-6 signaling. *Arthritis Rheum*. 2011;63:3575–85.
94. Kitaba S, Murota H, Terao M, et al. Blockade of interleukin-6 receptor alleviates disease in mouse model of scleroderma. *Am J Pathol*. 2012;80:165–76.
95. Shima Y, Kuwahara Y, Murota H, et al. The skin of patients with systemic sclerosis softened during the treatment with anti-IL-6 receptor antibody tocilizumab. *Rheumatology (Oxford)*. 2010;49:2408–12.
96. Kuwahara Y, Shima Y, Shirayama D, et al. Quantification of hardness, elastic and viscosity of the skin of patients with systemic sclerosis using a novel sensing device (Vesmeter): a proposal for a new outcome measurement procedure. *Rheumatology (Oxford)*. 2008;47:1018–24.
97. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol*. 2010;6:129–37.
98. Gabay C, Gay-Croisier F, Roux-Lombard P, et al. Elevated serum levels of interleukin-1 receptor antagonist in polymyositis/dermatomyositis. A biologic marker of disease activity with a possible role in the lack of acute-phase protein response. *Arthritis Rheum*. 1994;37:1744–51.
99. Lundberg I, Ulfgren AK, Nyberg P, Andersson U, Klareskog L. Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies. *Arthritis Rheum*. 1997;40:865–74.
100. Lepidi H, Frances V, Figarella-Branger D, Bartoli C, Machado-Baeta A, Pellissier JF. Local expression of cytokines in idiopathic inflammatory myopathies. *Neuropathol Appl Neurobiol*. 1998;24:73–9.
101. Sugiura T, Kawaguchi Y, Harigai M, et al. Increased CD40 expression on muscle cells of polymyositis and dermatomyositis: role of CD40-CD40 ligand interaction in IL-6, IL-8, IL-15, and monocyte chemoattractant protein-1 production. *J Immunol*. 2000;164:6593–600.
102. Scuderi F, Mannella F, Marino M, Provenzano C, Bartoccioni E. IL-6-deficient mice show impaired inflammatory response in a model of myosin-induced experimental myositis. *J Neuroimmunol*. 2006;176:9–15.
103. Okiyama N, Sugihara T, Iwakura Y, Yokozeki H, Miyasaka N, Kohsaka H. Therapeutic effects of interleukin-6 blockade in a murine model of polymyositis that does not require interleukin-17A. *Arthritis Rheum*. 2009;60:2505–12.
104. Narazaki M, Hagihara K, Shima Y, Ogata A, Kishimoto T, Tanaka T. Therapeutic effect of tocilizumab on two patients with polymyositis. *Rheumatology (Oxford)*. 2011;50:1344–6.
105. Langford CA. Vasculitis. *J Allergy Clin Immunol*. 2010;125:S216–25.
106. Sharma P, Sharma S, Baltaro R, Hurley J. Systemic vascultis. *Am Fam Physician*. 2011;83:556–65.
107. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*. 2008;372:234–45.
108. Mason JC. Takayasu arteritis-advances in diagnosis and management. *Nat Rev Rheumatol*. 2010;6:405–15.
109. Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. *Br J Rheumatol*. 1990;29:456–8.
110. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. *Arthritis Rheum*. 1993;36:1286–94.
111. Caplanne D, Le Parc JM, Alexandre JA. Interleukin-6 in clinical relapses of polymyalgia and giant cell arteritis. *Ann Rheum Dis*. 1996;55:403–4.
112. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. *Arthritis Rheum*. 2000;43:1041–8.

113. Garcia-Martinez A, Hernandez-Rodriguez J, Espigol-Frigole G, et al. Clinical relevance of persistently elevated circulating cytokines (tumor necrosis factor alpha and interleukin-6) in the long-term followup of patients with giant cell arteritis. *Arthritis Care Res.* 2010;62:835–41.
114. Noris M, Daina E, Gamba S, Bonazzola S, Remuzzi G. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? *Circulation.* 1999;100:55–60.
115. Park MC, Lee SW, Park YB, Lee SK. Serum cytokine profiles and their correlations with disease activity in Takayasu's arteritis. *Rheumatology (Oxford).* 2006;45:545–8.
116. Wagner AD, Goronzy JJ, Weyand CM. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis. Evidence for two components of the disease. *J Clin Invest.* 1994;94:1134–40.
117. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia and giant cell arteritis. *Ann Intern Med.* 1994;121:484–91.
118. Hernandez-Rodriguez J, Segarra M, Vilardell C, et al. Tissue production of pro-inflammatory cytokines (IL-1beta, TNFalpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. *Rheumatology (Oxford).* 2004;43: 294–301.
119. Seko Y, Sato O, Takagi A, et al. Restricted usage of T-cell receptor Valpha-Vbeta genes in infiltrating cells in aortic tissue of patients with Takayasu's arteritis. *Circulation.* 1996;93:1788–90.
120. Nishimoto N, Nakahara H, Yoshio-Hoshino N, Mima T. Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum.* 2008;58:1197–200.
121. Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med Wkly.* 2011;141:w13156.
122. Beyer C, Axmann R, Sahinbegovic E, et al. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann Rheum Dis.* 2011;70:1874–5.
123. Sciascia S, Rossi D, Roccatello D. Interleukin 6 blockade as steroid-sparing treatment for 2 patients with giant cell arteritis. *J Rheumatol.* 2011;38:2080–1.
124. Salvarani C, Magnani L, Catanoso M, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology (Oxford).* 2012;51: 151–6.
125. Vinit J, Bielefeld P, Muller G, Besancenot JF. Efficacy of tocilizumab in refractory giant cell arteritis. *Joint Bone Spine.* 2012;79:317–8.
126. Christidis D, Jain S, Das Gupta B. Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement. *BMJ Case Reports.* Jun 30, 2011:2011.
127. Besada E, Nossent JC. Ultrasonographic resolution of the vessel wall oedema with modest clinical improvement in a large-vessel vasculitis patient treated with tocilizumab. *Clin Rheumatol.* 2012;31:1263–5.
128. Salvarani C, Magnani L, Catanoso M, et al. Rescue treatment with tocilizumab for Takayasu arteritis resistant to TNF-α blockers. *Clin Exp Rheumatol.* 2012;30(1 Suppl 70):S90–3.
129. Bredemeier M, Rocha C, Barbosa M, Pitrez E. One-year clinical and radiological evolution of a patient with refractory Takayasu's arteritis under treatment with tocilizumab. *Clin Exp Rheumatol.* 2012;30(1 Suppl 70): S98–100.
130. Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. *Arthritis Res Care.* 2012;64:1720–9.
131. Lurati A, Bertani L, Re KA, Marrazza M, Bompane D, Scarpellini M. Successful treatment of a patient with giant cell vasculitis (horton arteritis) with tocilizumab a humanized anti-interleukin-6 receptor antibody. *Case Report Rheumatol.* 2012:639612.
132. Isik M, Kilic L, Dogan I, Calquneri M. Tocilizumab for giant cell arteritis: an amazing result. *Rheumatol Int.* Sep 11, 2012. [Epub ahead of print.]
133. Cohen C, Mekinian A, Saidenberg-Kermanach N, et al. Efficacy of tocilizumab in rituximab-refractory cryoglobulinemia vasculitis. *Ann Rheum Dis.* 2012;71:628–9.
134. Sumida K, Ubara Y, Suwabe T, et al. Complete remission of myeloperoxidase-antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis complicated with rheumatoid arthritis using a humanized anti-interleukin 6 receptor antibody. *Rheumatology (Oxford).* 2011;50:1928–30.
135. Alvarez-Rodriguez L, Lopez-Hoyos M, Mata C, et al. Circulating cytokines in active polymyalgia rheumatica. *Ann Rheum Dis.* 2010;69:263–69.
136. Zen-Nyoji A, Shimizu H, Ohtani K, Oshimoto K, Kobayashi Y, Mori M. Increased RAHA titer and interleukin-6 levels in the synovial fluid in a patient with polymyalgia rheumatica. *Intern Med.* 1993;32:484–6.
137. Kreiner F, Langberg H, Galbo H. Increased muscle interstitial levels of inflammatory cytokines in polymyalgia rheumatica. *Arthritis Rheum.* 2010;62:3768–75.
138. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. *Arthritis Rheum.* 1997;40:1873–8.
139. Mazzantini M, Torre C, Miccoli M, et al. Adverse events during long-term low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. *J Rheumatol.* 2012;39:552–7.
140. Hagihara K, Kawase I, Tanaka T, Kishimoto T. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. *J Rheumatol.* 2010;37: 1075–6.
141. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. Systemic lupus erythematosus. *Lancet.* 2001;357:1027–32.
142. Obermoser G, Pascual V. The interferon-α signature of systemic lupus erythematosus. *Lupus.* 2010;19:1012–9.
143. Shin MS, Lee N, Kang I. Effector T-cell subsets in systemic lupus erythematosus: update focusing on Th17 cells. *Curr Opin Rheumatol.* 2011;23: 444–8.
144. Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. *Lupus.* 2004;13:339–43.
145. Linker-Israeli M, Deans RJ, Wallace DJ, Prehn J, Ozeri-Chen T, Klinenberg JR. Elevated levels of endogenous IL-6 in systemic lupus erythematosus: a putative role in pathogenesis. *J Immunol.* 1991;147: 117–23.
146. Peterson E, Robertson AD, Emlen W. Serum and urinary interleukin-6 in systemic lupus erythematosus. *Lupus.* 1996;5:571–5.
147. Grondal G, Gunnarsson I, Ronnelid J, Rogberg S, Klareskog L. Lundberg I. Cytokine production, serum levels and disease activity in systemic lupus erythematosus. *Clin Exp Rheumatol.* 2000;18:565–70.
148. Iwano M, Dohi K, Hirata E, et al. Urinary levels of IL-6 in patients with active lupus nephritis. *Clin Nephrol.* 1993;40:16–21.
149. Hirohata S, Miyamoto T. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. *Arthritis Rheum.* 1990;33:644–9.
150. Hagiwara E, Gourley MF, Lee S, Klinman DK. Disease severity in patients with systemic lupus erythematosus correlates with an increased ratio of interleukin-10:interferon-gamma-secreting cells in the peripheral blood. *Arthritis Rheum.* 1996;39:379–85.
151. Klashman DJ, Martin RA, Martinez-Maza O, Stevens RH. In vitro regulation of B cell differentiation by interleukin-6 and soluble CD23 in systemic lupus erythematosus B cell subpopulations and antigen-induced normal B cells. *Arthritis Rheum.* 1991;34:276–86.
152. Kitani A, Hara M, Hirose T, et al. Autostimulatory effects of IL-6 on excessive B cell differentiation in patients with systemic lupus erythematosus: analysis of IL-6 production and IL-6R expression. *Clin Exp Immunol.* 1992;88:75–83.
153. Ryffel B, Car BD, Gunn H, Roman D, Hiestand P, Mihatsch MJ. Interleukin-6 exacerbates glomerulonephritis in (NZB × NZW)F1 mice. *Am J Pathol.* 1994;144:927–37.
154. Finck BK, Chan B, Wofsy D. Interleukin 6 promotes murine lupus in NZB/NZW F1 mice. *J Clin Invest.* 1994;94:585–91.
155. Mihara M, Takagi N, Takeda Y, Ohsugi Y. IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F1 mice. *Clin Exp Immunol.* 1998;112:397–402.

156. Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XY. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. *Immunology*. 2006;119:296–305.
157. Pflegerl P, Vesely P, Hantusch B, et al. Epidermal loss of JunB leads to a SLE phenotype due to hyper IL-6 signaling. *Proc Natl Acad Sci U S A*. 2009;106:20423–8.
158. Illei GG, Shirota Y, Yarboro CH, et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum*. 2010;62:542–52.
159. Maeshima K, Ishii K, Torigoe M, et al. Successful tocilizumab and tacrolimus treatment in a patient with rheumatoid arthritis complicated by systemic lupus erythematosus. *Lupus*. 2012;21:1003–6.
160. Makol A, Gibson LE, Michet CJ. Successful use of interleukin 6 antagonist tocilizumab in a patient with refractory cutaneous lupus and urticarial vasculitis. *J Clin Rheumatol*. 2012;18:92–5.
161. Rapini RP, Warner NB. Relapsing polychondritis. *Clin Dermatol*. 2006;24: 482–5.
162. Lahmer T, Treiber M, von Werder A, et al. Relapsing polychondritis: an autoimmune disease with many faces. *Autoimmu Rev*. 2010;9:540–6.
163. Arnaud L, Devilliers H, Peng SL, et al. The relapsing polychondritis disease activity index: development of a disease activity score for relapsing polychondritis. *Autoimmun Rev*. 2012;12:204–9.
164. Stabler T, Piette JC, Chevalier X, Marini-Portugal A, Kraus VB. Serum cytokine profiles in relapsing polychondritis suggest monocyte/macrophage activation. *Arthritis Rheum*. 2004;50:3663–7.
165. Kemta Lekpa F, Kraus VB, Chevalier X. Biologics in relapsing polychondritis: a literature review. *Semin Arthritis Rheum*. 2012;41: 712–9.
166. Kawai M, Hagihara K, Hirano T, et al. Sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in two patients with refractory relapsing polychondritis. *Rheumatology (Oxford)*. 2009;48:318–9.
167. Narshi CB, Allard SA. Sustained response to tocilizumab, anti-IL-6 antibody, following anti-TNF-α failure in a patient with relapsing polychondritis complicated by aortitis. *Rheumatology (Oxford)*. 2012;51: 952–23.
168. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. 2005;202:473–7.
169. Ratelade J, Verkman AS. Neuromyelitis optica: Aquaporin-4 based pathogenesis mechanisms and new therapies. *Int J Biochem Cell Biol*. 2012;44: 1519–30.
170. Benarroch EE. Aquaporin-4, homeostatis, and neurologic disease. *Neurology*. 2007;69:2266–8.
171. Uzawa A, Mori M, Ito M, et al. Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. *J Neurol*. 2009;256:2082–4.
172. Icoz S, Tuzun E, Kurtuncu M, et al. Enhanced IL-6 production in aquaporin-4 antibody positive neuromyelitis optica patients. *Int J Neurosci*. 2010;120:71–5.
173. Uzawa A, Mori M, Arai K, et al. Cytokine and chemokine profiles in neuromyelitis optica: significance of interleukin-6. *Mult Scler*. 2010;16: 1443–52.
174. Wang H, Wang K, Zhong X, et al. Notable increased cerebrospinal fluid levels of soluble interleukin-6 receptors in neuromyelitis optica. *Neuroimmunomodulation*. 2012;19:304–8.
175. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proc Natl Acad Sci U S A*. 2011;108:3701–6.
176. Araki M, Aranami T, Matsuoka T, Nakamura M, Miyake S, Yamamura T. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab. *Mod Rheumatol*. Jul 11, 2012. [Epub ahead of print.]
177. Kieseier BC, Stuve O, Dehmel T, et al. Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implication for cellular immune responses. *Arch Neurol*. Dec 24, 2012. [Epub ahead of print.]
178. Shanahan F. Crohn's disease. *Lancet*. 2002;359:62–9.
179. Perrier C, Rutgeerts P. Cytokine blockade in inflammatory bowel diseases. *Immunotherapy*. 2011;3:1341–52.
180. Holub MC, Mako E, Devay T, et al. Increased interleukin-6 levels, interleukin-6 receptor and gp130 expression in peripheral lymphocytes of patients with inflammatory bowel disease. *Scand J Gastroenterol Suppl*. 1998;228:47–50.
181. Hosokawa T, Kusugami K, Ina K, et al. Interleukin-6 and soluble interleukin-6 receptor in the colonic mucosa of inflammatory bowel disease. *J Gastroenterol Hepatol*. 1999;14:987–96.
182. Van Kemseke C, Belaiche J, Louis E. Frequently relapsing Crohn's disease is characterized by persistent elevation in interleukin-6 and soluble interleukin-2 receptor serum levels during remission. *Int J Colorectal Dis*. 2000;15:206–10.
183. Yamamoto M, Yoshizaki K, Kishimoto T, Ito H. IL-6 is required for the development of Th1 cell-mediated murine colitis. *J Immunol*. 2000;164: 4878–82.
184. Ito H, Takazoe M, Fukuda Y, et al. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology*. 2004;126:989–96.
185. Efthimiou P, Kontzias A, Ward CM, Ogden NS. Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy? *Nat Clin Pract Rheumatol*. 2007;3:328–35.
186. Fautrel B. Adult-onset Still disease. *Best Pract Res Clin Rheumatol*. 2008;22:773–92.
187. Scheinberg MA, Chapira E, Fernades ML, Hubscher O. Interleukin 6: a possible marker of disease activity in adult onset Still's disease. *Clin Exp Rheumatol*. 1996;14:653–5.
188. Hoshino T, Ohta A, Yang D, et al. Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease. *J Rheumatol*. 1998;25:396–8.
189. Fujii T, Nojima T, Yasuoka H, et al. Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease. *Rheumatology (Oxford)*. 2001;40:1398–404.
190. Choi JH, Suh CH, Lee YM, et al. Serum cytokine profiles in patients with adult onset Still's disease. *J Rheumatol*. 2003;30:2422–7.
191. Iwamoto M, Nara H, Hirata D, Minota S, Nishimoto N, Yoshizaki K. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. *Arthritis Rheum*. 2002;46: 3388–9.
192. Nakahara H, Mima T, Yoshio-Hoshino N, Matsushita M, Hashimoto J, Nishimoto N. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. *Mod Rheumatol*. 2009;19:69–72.
193. De Bandt M, Saint-Marcoux B. Tocilizumab for multirefractory adult-onset Still's disease. *Ann Rheum Dis*. 2009;68:153–4.
194. Matsumoto K, Nagashima T, Takatori S, et al. Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. *Clin Rheumatol*. 2009;28:485–7.
195. Cunha ML, Wagner J, Osawa A, Scheinberg M. The effect of tocilizumab on the uptake of 18FDG-PET imaging in patients with adult-onset Still's disease. *Rheumatology (Oxford)*. 2010;49:1014–6.
196. Sumida K, Ubara Y, Hoshino J, et al. Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab. *Clin Rheumatol*. 2010;29:1191–4.
197. Yoshimura M, Makiyama J, Koga T, Miyashita T, Izumi Y, Torigoshi T, et al. Successful treatment with tocilizumab in a patient with refractory adult-onset Still's disease (AOSD). *Clin Exp Rheumatol*. 2010;28:141–2.
198. Perdan-Pirkmajer K, Praprotnik S, Tomsic M. A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature. *Clin Rheumatol*. 2010;29:1465–7.
199. Naniwa T, Ito R, Watanabe M, et al. Case report: successful use of short-term add-on tocilizumab for multirefractory systemic flare of adult-onset Still's disease. *Clin Rheumatol*. Sep 15, 2010. [Epub ahead of print.]
200. Kishida D, Okuda Y, Onishi M, et al. Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis. *Mod Rheumatol*. 2011;21: 215–8.

201. Thonhofer R, Hiller M, Just H, Trummer M, Siegel C, Dejaco C. Treatment of refractory adult-onset Still's disease with tocilizumab: report of two cases and review of the literature. *Rheumatol Int.* 2011;31:1653–6.
202. Sabnis GR, Gokhale YA, Kulkarni UP. Tocilizumab in refractory adult-onset Still's diseases with aseptic meningitis-efficacy of interleukin-6 blockade and review of the literature. *Semin Arthritis Rheum.* 2011;40:365–8.
203. Rech J, Ronneberger M, Englbrecht M, et al. Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 blockade. *Ann Rheum Dis.* 2011;70:390–2.
204. Kobayashi M, Takahashi Y, Yamashita H, Kaneko H, Mimori A. Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macrophage-activation syndrome. *Mod Rheumatol.* 2011;21:92–6.
205. Puechal X, DeBandt M, Berthelot JM, et al. Tocilizumab in refractory adult Still's disease. *Arthritis Care Res.* 2011;63:155–9.
206. Sekkach Y, Elqatni M, Khattabi AE, et al. Antagonists of interleukin-6 (tocilizumab) in adult refractory still disease. *Presse Med.* 2011;40: e333–7.
207. Suematsu R, Ohta A, Matsuura E, et al. Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan. *Mod Rheumatol.* 2012;22:712–9.
208. Perfetto F, Moggi-Pignone A, Livi R, Tempestini A, Bergesio F, Matucci-Cerinic M. Systemic amyloidosis: a challenge for the rheumatologist. *Nat Rev Rheumatol.* 2010;6:417–29.
209. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med.* 2007;356:2361–71.
210. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet.* 2001;358:24–9.
211. Hagihara K, Nishikawa T, Isobe T, Song J, Sugamata Y, Yoshizaki K. IL-6 plays a critical role in the synergistic induction of human serum amyloid A (SAA) gene when stimulated with proinflammatory cytokines as analyzed with an SAA isoform real-time quantitative RT-PCR assay system. *Biochem Biophys Res Commun.* 2004;314:363–9.
212. Hagihara K, Nishikawa T, Sugamata Y, et al. Essential role of STAT3 in cytokine-driven NF-kappaB-mediated serum amyloid A gene expression. *Genes Cells.* 2005;10:1051–63.
213. Nishimoto N, Yoshizaki K, Maeda K, et al. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. *J Rheumatol.* 2003;30:1426–35.
214. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2004;50: 1761–9.
215. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood.* 2005;106:2627–32.
216. Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. *Arthritis Rheum.* 2006;54:2997–3000.
217. Nishida S, Hagihara K, Shima Y, et al. Rapid improvement of AA amyloidosis with humanised anti-interleukin 6 receptor antibody treatment. *Ann Rheum Dis.* 2009;68:1235–6.
218. Sato H, Sakai T, Sugaya T, et al. Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis. *Clin Rheumatol.* 2009;28:1113–6.
219. Inoue D, Arima H, Kawanami C, et al. Excellent therapeutic effect of tocilizumab on intestinal amyloid a deposition secondary to active rheumatoid arthritis. *Clin Rheumatol.* 2010;29:1195–7.
220. De La Torre M, Arboleya L, Pozo S, Pinto J, Velasco J. Rapid and sustained response to tocilizumab, amti-interleukin-6 receptor antibody, in a patient with nephritic syndrome secondary to systemic juvenile idiopathic arthritis-related amyloidosis. *NDT Plus.* 2011;4:178–80.
221. Magro-Checa C, Navas-Parejo Casado A, Borrego-Garcia E, et al. Successful use of tocilizumab in a patient with nephritic syndrome due to a rapidly progressing AA amyloidosis to latent tuberculosis. *Amyloid.* 2011;18:235–9.
222. Hattori Y, Ubara Y, Sumida K, et al. Tocilizumab improves cardiac disease in a hemodialysis patient with AA amyloidosis secondary to rheumatoid arthritis. *Amyloid.* 2012;19:37–40.
223. Tanaka T, Hagihara K, Hishitani Y, Ogata A. Tocilizumab for the treatment of AA amyloidosis. In: Guvenc IA, editor. Amyloidosis—An insight to disease of systems and novel therapies. Croatia: INTECH Open Access Publisher; 2011:155–70.
224. Mendes D, Correia M, Barbedo M, Vaio T, Mota M. Behcet's disease-a contemporary review. *J Autoimmun.* 2009;32:178–88.
225. Hirohata S, Oka H, Mizushima Y. Streptococcal-related antigens stimulate production of IL-6 and interferon-gamma by T cells from patients with Behcet's disease. *Cell Immunol.* 1992;140:410–9.
226. Mege JL, Dilsen N, Sanguedolce V, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behcet's disease. A comparative study with familial Mediterranean fever and healthy subjects. *J Rheumatol.* 1993;20:1544–9.
227. Yamakawa Y, Sugita Y, Nagatani T, et al. Interleukin-6 (IL-6) in patients with Behcet's disease. *J Dermatol Sci.* 1996;11:189–95.
228. Kulaber A, Tugal-Tutkun I, Yentur SP, et al. Pro-inflammatory cellular immune response in Behcet's disease. *Rheumatol Int.* 2007;27:1113–8.
229. Hirano T, Ohguro N, Hohki S, et al. A case of Behcet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod Rheumatol.* 2012;22:298–302.
230. Hirohata S, Isshi K, Oguchi H, et al. Cerebrospinal fluid interleukin-6 in progressive neuro-Behcet's syndrome. *Clin Immunol Immunopathol.* 1997;82:12–7.
231. Akman-Demir G, Turun E, Icoz S, et al. Interleukin-6 in neuro-Behcet's disease: association with disease subsets and long-term outcome. *Cytokine.* 2008;44:373–6.
232. Borhani Haghighi A, Ittehadi H, Nikseresht AR, et al. CSF levels of cytokines in neuro-Behcet's disease. *Clin Neurol Neurosurg.* 2009;111:507–10.
233. Shapiro LS, Farrell J, Haghighi AB. Tocilizumab treatment for neuro-Behcet's disease, the first report. *Clin Neurol Neurosurgery.* 2012;114: 297–8.
234. Caspi RR. A look at autoimmunity and inflammation in the eye. *J Clin Invest.* 2010;120:3073–83.
235. Murray PI, Hoekzema R, van Haren MA, de Hon FD, Kijlstra A. Aqueous humor interleukin-6 levels in uveitis. *Invest Ophthalmos Vis Sci.* 1990;31: 917–20.
236. Benson MT, Shepherd L, Rees RC, Rennie IG. Production of interleukin-6 by human retinal pigment epithelium in vitro and its regulation by other cytokines. *Curr Eye Res.* 1992;11(Suppl):173–9.
237. Norose K, Yano A, Wang XC, et al. Dominance of activated T cells and interleukin-6 in aqueous humor in Vogt-Koyanagi-Harada disease. *Invest Ophthalmol Vis Sci.* 1994;35:33–9.
238. Petrinovic-Doresic J, Mazuran R, Henc-Petrinovic L, Kuzmanovic B, Jovicic A. Interleukin 6 and its soluble receptor are elevated in aqueous humor of patients with uveitis. *Ocul Immunol Inflamm.* 1999;7:75–84.
239. Perez VL, Papaliodis GN, Chu D, Anzaar F, Christen W, Foster CS. Elevated levels of interleukin 6 in the vitreous fluid of patients with pars planitis and posterior uveitis: the Massachusetts eye and ear experience and review of previous studies. *Ocul Immunol Inflamm.* 2004;12:193–201.
240. Yoshimura T, Sonoda K, Ohguro N, et al. Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. *Rheumatology (Oxford).* 2009;48:347–54.
241. Hohki S, Ohguro N, Haruta H, et al. Blockade of interleukin-6 signaling suppresses experimental autoimmune uveoretinitis by the inhibition of inflammatory Th17 responses. *Exp Eye Res.* 2010;91:162–70.
242. Haruta H, Ohguro N, Fujimoto M, et al. Blockade of interleukin-6 signaling suppresses not only Th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis. *Invest Ophthalmol Vis Sci.* 2011;52: 3264–71.
243. Muselier A, Bielefeld P, Bidot S, Vinit J, Besancenot JF, Bron A. Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. *Ocul Immunol Inflamm.* 2011;19:382–3.

244. Gergis U, Arnason J, Yantiss R, et al. Effectiveness and safety of tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, in a patient with refractory GI graft-versus-host disease. *J Clin Onocol.* 2010;28:e602–4.
245. Drobyski WR, Pasquini M, Kovatovic K, et al. Tocilizumab for the treatment of steroid refractory graft versus host disease. Biol *Blood Marrow Transplant.* 2011;17:1862–8.
246. Nishida S, Kawasaki T, Kashiwagi H, et al. Successful treatment of acquired hemophilia A, complicated by chronic GVHD, with tocilizumab. *Mod Rheumatol.* 2011;21:420–2.
247. Kunitomi A, Konaka Y, Yagita M, Nishimoto N, Kishimoto T, Takatsuki K. Humanized anti-interleukin 6 receptor antibody induced long-term remission in a patient with life-threatening refractory autoimmune hemolytic anemia. *Int J Hematol.* 2004;80:246–9.
248. Yuzuriha A, Saitoh T, Koiso H, et al. Successful treatment of autoimmune hemolytic anemia associated with multicentric Castleman disease by anti-interleukin-6 receptor antibody (tocilizumab) therapy. *Acta Haematol.* 2011;126:147–50.
249. Garcia-Hernandez FJ, Gonzalez-Leon R, Castillo-Palma MJ, Ocana-Medina C, Sanchez-Roman J. Tocilizumab for treating refractory haemolytic anaemia in a patient with systemic lupus erythematosus. *Rheumatology (Oxford).* 2012;51:1918–9.
250. Tanaka T, Hagihara K, Shima Y, et al. Treatment of a patient with remitting seronegative, symmetrical synovitis with pitting oedema with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Rheumatology (Oxford).* 2010;49:824–6.
251. Furuya Y, Satoh T, Kuwana M. Interleukin-6 as a potential therapeutic target for pulmonary arterial hypertension. *Int J Rheumatol.* 2010:Article ID 720305.
252. Taniguchi K, Shimazaki C, Fujimoto Y, et al. Tocilizumab is effective for pulmonary hypertension associated with multicentric Castleman's disease. *Int J Hematol.* 2009;90:99–102.
253. Arita Y, Sakata Y, Sudo T, et al. The efficacy of tocilizumab in a patient with pulmonary arterial hypertension associated with Castleman's disease. *Heart Vessels.* 2010;25:444–7.
254. Vaitla PM, Radford PM, Tighe PJ, et al. Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the anti-interleukin-6 receptor monoclonal antibody tocilizumab. *Arthritis Rheum.* 2011;63:1151–5.
255. Navarini AA, French LE, Hofbauer GFL. Interrupting IL-6-receptor signaling improves atopic dermatitis but associates with bacterial superinfection. *J Allergy Clin Immunol.* 2011;128:1128–30.
256. Schanz S, Schmalzing M, Guenova E, et al. Interstitial granulomatous dermatitis with arthritis responding to tocilizumab. *Arch Dermatol.* 2012;148:17–20.
257. Ohtori S, Miyagi M, Eguchi Y, et al. Efficacy of epidural administration of anti-interleukin-6 receptor antibody onto spinal nerve for treatment of sciatica. *Eur Spine J.* 2012;21:2079–84.
258. Henes JC, Horger M, Guenaydin I, Kanz L, Koetter I. Mixed response to tocilizumab for ankylosing spondylitis. *Ann Rheum Dis.* 2010;69:2217–8.
259. Wendling D, Bossert M, Prati C. Short-term effect of IL-6 inhibition in spondylarthritis. *Joint Bone Spine.* 2010;77:624–5.
260. Brulhart L, Nissen MJ, Chevallier P, Gabay C. Tocilizumab in a patient with ankylosing spondylitis and Crohn's disease refractory to TNF antagonists. *Joint Bone Spine.* 2010;77:625–6.
261. Shima Y, Tomita T, Ishii T, et al. Tocilizumab, a humanized anti-interleukin-6 receptor antibody, ameliorated clinical symptoms and MRI findings of a patient with ankylosing spondylitis. *Mod Rheumatol.* 2011;21:436–9.
262. Cohen JD, Ferreira R, Jorgensen C. Ankylosing spondylitis refractory to tumor necrosis factor blockade responds to tocilizumab. *J Rheumatol.* 2011;38:1527.
263. Tanaka T, Kuwahara Y, Shima Y, et al. Successful treatment of reactive arthritis with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Arthritis Rheum.* 2009;61:1762–4.
264. Kwan K, Bharadwaj S, Inderjeeth C. Response to treatment with tocilizumab of reactive arthritis induced by intravesical bacillus Galmette-Guerin unresponsive to DMARDs. *Int J Rheum Dis.* 2012;15:e73–5.
265. Sieper J, Inman RD, Badalamenti S, Radin A, Braun J. Sarilumab for the treatment of ankylosing spondylitis: results of phase 2, randomized double-blind, placebo-controlled, international study (ALIGN). *Ann Rheum Dis.* 2012;71(Suppl 3):111.
266. Ogata A, Morishima A, Hirano T, et al. Improvement of HbA1c during treatment with humanised anti-interleukin 6 receptor antibody, tocilizumab. *Ann Rheum Dis.* 2011;70:1164–5.
267. Schultz O, Oberhauser F, Saech J, et al. Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS One.* 2010;5:e14328.
268. Hirao M, Yamasaki N, Oze H, et al. Serum level of oxidative stress marker is dramatically low in patients with rheumatoid arthritis treated with tocilizumab. *Rheumatol Int.* 2012;32:4041–4015.
269. Matthijs Boekholdt S, Stores ESG. The interleukin-6 pathway and atherosclerosis. *Lancet.* 2012;379:1176–8.
270. Qin Z, Keamey P, Plaisance K, Parsons CH. Pivotal advance: Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNA specifically induce IL-6 and IL-10 secretion by macrophages and monocytes. *J Leukoc Biol.* 2010;87:25–34.
271. Leung K, Nabel GJ. HTLV-1 transactivator induces interleukin-2 receptor expression through an NF-kappa B-like factor. *Nature.* 1988;333:776–8.
272. Ballard DW, Bohnlein E, Lowenthal JW, Wano Y, Franza BR, Greene WC. HTLV-1 tax induces cellular proteins that activate the kappa B element in the IL-2 receptor alpha gene. *Science.* 1988;241:1652–5.
273. Scala G, Ruocco MR, Ambrosino C, et al. The expression of the interleukin 6 gene is induced by the human immunodeficiency virus 1 TAT protein. *J Exp Med.* 1994;179:961–71.
274. Ambrosino C, Ruocco MR, Chen X, et al. HIV-1 Tat induces the expression of the interleukin-6 (IL6) gene by binding to the IL6 leader RNA and by interacting with CAAT enhancer-binding protein beta (NF-IL6) transcription factors. *J Biol Chem.* 1997;272:14883–92.
275. Mahe Y, Mukaida N, Kuno K, et al. Hepatitis B virus X protein transactivates human interleukin-8 gene through acting on nuclear factor kB and CCAAT/enhancer-binding protein-like cis-elements. *J Biol Chem.* 1991;266:13759–63.
276. Ohno H, Kaneko S, Lin Y, Kobayashi K, Murakami S. Human hepatitis B virus X protein augments the DNA binding of nuclear factor for IL-6 through its basic-leucine zipper domain. *J Med Virol.* 1999;58:11–8.

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ORIGINAL ARTICLE

Clinical characteristics and risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case–control study of 17 patients

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Abstract
Objectives To investigate the clinical characteristics and risk factors of *Pneumocystis jirovecii* pneumonia (PCP) in rheumatoid arthritis (RA) patients treated with adalimumab.

Methods We conducted a multicenter, retrospective, case–control study to compare RA patients treated with adalimumab with and without PCP. Data from 17 RA patients who were diagnosed with PCP and from 89 RA

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patients who did not develop PCP during adalimumab treatment were collected.
Results For the PCP patients, the median age was 68 years old, with a median RA disease duration of eight years. The median length of time from the first adalimumab injection to the development of PCP was 12 weeks. At the onset of PCP, the median dosages of prednisolone and methotrexate were 5.0 mg/day and 8.0 mg/week, respectively. The patients with PCP were significantly older ($p < 0.05$) and had more structural changes ($p < 0.05$) than the patients without PCP. Computed tomography of the chest revealed ground-glass opacity without interlobular septal boundaries in the majority of the patients with PCP. Three PCP patients died.
Conclusions PCP may occur early in the course of adalimumab therapy in patients with RA. Careful monitoring, early diagnosis, and proper management are mandatory to secure a good prognosis for these patients.

Keywords Adalimumab · *Pneumocystis jirovecii* pneumonia · Rheumatoid arthritis · TNF antagonist

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by persistent synovitis and structural damage to multiple joints. Tumor necrosis factor (TNF) is abundantly produced in the inflamed synovium and contributes to the imuunopathogenesis of the disease. Adalimumab is the first fully human monoclonal antibody against TNF; treatment with this biologic agent has been well established in patients with RA in multiple clinical trials [1–3]. On the other hand, treatment with adalimumab, as well as infliximab and etanercept, has been associated with increased risk for opportunistic and serious infections in cohort studies using RA patient registries [4–7]. In Japan, strict post-marketing surveillance (PMS) programs have been conducted for patients with RA given TNF antagonists. The numbers of RA patients with *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia (PCP) who were treated with infliximab, etanercept, or adalimumab were 22 (0.4 %) out of 5,000 patients, 25 (0.18 %) out of 13,894 patients, and 25 (0.33 %) out of 7,469 patients, respectively, in these PMS programs [6–8]. Note that these incidence rates of PCP in Japan are apparently higher than the corresponding figure (0.01 %) reported from the United States [9].

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We have previously described the clinical characteristics and risk factors for PCP in RA patients treated with infliximab [10, 11] and etanercept [12]. These risk factors included older age and presence of coexisting lung diseases for both TNF antagonists, a higher daily dose of prednisolone (PSL) for infliximab, and a higher weekly dose of methotrexate (MTX) for etanercept. Considering the similar incidence of PCP in the PMS programs among the three TNF antagonists, it is clinically important and intriguing to characterize PCP in RA patients given adalimumab and to compare the results with those obtained for RA patients treated with other TNF antagonists.

In this paper, we report detailed clinical, laboratory, and radiographic features of PCP that developed in RA patients during treatment with adalimumab. Furthermore, we compared 17 RA patients receiving adalimumab who developed PCP with 89 RA patients who did not develop PCP during treatment, and identified risk factors for PCP in patients with RA treated with adalimumab.

Materials and methods

Patients

Patients included in the present study fulfilled the 1987 American College of Rheumatology (formerly the American Rheumatism Association) criteria for RA [13] and received adalimumab (40 mg every two weeks) with or without concomitant MTX. Between April 2008 and April 2010, 17 patients with PCP (PCP group) were collected from 16 hospitals through either the PMS program for adalimumab ($n = 16$) or through a voluntary case report by attending physicians at a scientific meeting ($n = 1$). We convened a face-to-face meeting in March 2011 to discuss diagnosis and treatment for the collected cases among the investigators of this study. RA patients who did not develop PCP during adalimumab therapy for at least one year from the first dose of adalimumab (non-PCP group, $n = 89$) were randomly collected from the participating hospitals of this study. Other eligibility criteria for the non-PCP group were registration in the PMS program of adalimumab and the use of adalimumab five times or more. The median (range) observation period for the non-PCP group treated with adalimumab was 365 (63–365) days. To increase the statistical power of this case–control study, the number of patients in the non-PCP group was designed to be about five times as many as that in the PCP group [14].

Diagnostic criteria for PCP

Previously established diagnostic criteria for PCP [15, 16] were used in the present study [10]. A diagnosis of PCP was considered definitive if a patient fulfilled the following four conditions: clinical manifestations (fever, dry cough, or dyspnea), hypoxemia, interstitial infiltrates on chest radiographs, and microscopic detection of *P. jirovecii* in induced sputum or bronchoalveolar lavage fluid. The diagnosis of PCP was considered presumptive if a patient fulfilled all of these conditions except for the microscopic detection of *P. jirovecii* in the absence of other infectious diseases and the presence of either a positive polymerase chain reaction (PCR) test for *P. jirovecii* DNA or increased serum 1,3-β-D-glucan (BDG) levels (Fungitec G test MK; Seikagaku, Tokyo, Japan or Wako β-D-glucan test; Wako Pure Chemical Industries, Tokyo, Japan) [17, 18] along with a response to standard treatments for PCP. Both the PCR test for *P. jirovecii* DNA and that for serum BDG are commercially available, validated, and officially approved as clinical laboratory tests by the Ministry of Health, Labour, and Welfare in Japan.

Collection and analysis of clinical data

Clinical information was collected using a standardized format to evaluate demographic information, Steinbrocker's radiographic stage and functional class [19], comorbidities, concomitant drugs, laboratory data, radiographic data, treatment, and outcome. Chest radiographs and computed tomography (CT) scans were evaluated by a pulmonologist (H.S.) and a diagnostic radiologist (F.S.). CT findings were categorized into three patterns, as we did in previous studies [12, 20]: (a) diffuse ground-glass opacity (GGO) distributed in a panlobular manner; that is, GGO was sharply demarcated from the adjacent normal lung by interlobular septa (type A GGO); (b) diffuse GGO that is homogeneous or somewhat inhomogeneous in distribution but without the sharp demarcation caused by interlobular septa (type B GGO); (c) other patterns, such as mixed consolidation and GGO (type C).

Statistical analyses

Demographic data and baseline data were compared between the PCP and non-PCP groups using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables. To identify risk factors for PCP, the Cox proportional-hazards regression model was used. All analyses were performed using SPSS software, version 16.0 (SPSS Japan, Tokyo, Japan).

Ethics

The guidelines of the Declaration of Helsinki (revised in 2008) and the ethics guidelines for epidemiologic research in Japan were followed. The study protocol was approved

by the Institutional Ethics Committee of the Tokyo Medical and Dental University Hospital (#863 in 2010).

Results

Diagnosis and clinical characteristics of RA patients with PCP

We applied the above diagnostic criteria to the 17 RA patients in the PCP group. Of the 17 cases, three (patients 8, 14, and 17) met the criteria for definitive PCP, and 14 met the criteria for presumptive PCP. The clinical characteristics of each patient are summarized in Table 1. The median age of the 17 patients was 68 years (range 48–78 years), and 12 (71 %) were female. The median duration of RA was eight years. Fourteen patients were at Steinbrocker's stage III or IV. All patients received MTX and 13 (77 %) received corticosteroids from baseline to the onset of PCP. At the onset of PCP, the median dosages of prednisolone and MTX were 5.0 mg/day (range 2.5–9 mg/day) and 8.0 mg/week (range 4–15 mg/week), respectively. One patient was receiving another immunosuppressive drug, tacrolimus, at 3 mg/day. Eight patients had pulmonary comorbidities, including interstitial pneumonia ($n = 4$), chronic obstructive pulmonary disease ($n = 4$), and old pulmonary tuberculosis ($n = 2$). Four patients had diabetes mellitus. None of the patients received chemoprophylaxis for PCP at the time of PCP diagnosis. The median interval between the first injection of adalimumab and the onset of PCP was 12 weeks (range 4–38 weeks). Thirteen patients (76 %) developed PCP within 26 weeks after the first injection. Fever was the most common clinical symptom (it was observed in 15 patients; 88 %), followed by dyspnea on effort (82 %) and dry cough (41 %).

Laboratory and radiographic features of the PCP patients

Laboratory data at the onset of PCP are summarized in Table 2. Fourteen patients either had severe hypoxia (with $PaO_2 < 60$ mm Hg on room air) or required immediate oxygen therapy at the onset of PCP. Peripheral blood lymphocyte (PBL) counts at the onset of PCP were <500 cells/μl in three patients, 500–1,000 cells/μl in five patients, and $>1{,}000$ cells/μl in nine patients. *P. jirovecii* was microscopically identified in three patients. The polymerase chain reaction test for *P. jirovecii* DNA was positive in 13 patients, using either induced sputum (11 patients) or bronchoalveolar lavage fluid (four patients), but three patients were not examined. Serum levels of BDG, one of

Table 1 Characteristics of rheumatoid arthritis patients treated with adalimumab at the onset of PCP

Pt	Age/sex	Stage/class	Number of injections[a]	Treatment duration (days)[b]	MTX (mg/w)	PSL (mg/d)	Lung disease	DM	Clinical manifestations
1	48/F	III/I	7	105	8	2.5	–	–	Fever/DOE
2	69/M	IV/III	4	62	10	0	E	–	Cough/DOE
3	74/F	IV/II	9	131	8	5	IP E	–	DOE
4	52/M	III/II	5	59	4	8	IP	–	Fever/cough/DOE
5	61/F	IV/II	3	45	8	9	–	–	Fever
6	67/F	III/III	3	28	8	8	IP	–	Fever/cough/DOE
7	61/F	IV/II	4	59	6	0	Old TB	–	Fever/DOE
8	77/F	IV/II	6	129	6	5	–	+	Fever/DOE
9	52/F	III/I	3	55	8	5	–	–	Fever/DOE
10	78/M	III/III	6	86	8	0	IP	+	Fever/DOE
11	66/F	I/III	6	106	8	3	–	–	Fever/cough
12	70/F	II/II	2	23	8	5	Old TB	–	Fever/cough/DOE
13	68/M	I/II	3	28	8	0	E	+	Fever/DOE
14	71/F	III/II	15	214	8	7.5	–	–	Fever/DOE
15	73/M	III/II	18	268	15	3	–	+	Fever/cough/DOE
16	65/F	III/II	16	227	8	2	–	–	Fever/DOE
17	78/F	IV/II	16	252	4	4	–	–	Fever/cough

PCP Pneumocystis jirovecii pneumonia, *Pt* patient, *w* week, *d* day, *M* male, *F* female, *MTX* methotrexate, *PSL* prednisolone, *E* emphysema, *IP* interstitial pneumonia, *old TB* old tuberculosis, *DM* diabetes mellitus, *DOE* dyspnea on effort, *cough* dry cough

[a] Number of injections of ADA prior to the diagnosis of PCP

[b] Treatment duration with ADA before the onset of PCP