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REVIEW ARTICLE

A new alternative therapy in dermatology: tocilizumab

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Abstract

Tocilizumab (TCZ) is a recombinant-humanized anti-human interleukin 6 receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure. Even if it was approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis, satisfying results have also been reported with TCZ in various refractory dermatological diseases such as psoriasis, psoriatic arthritis, Behçet's disease, systemic lupus erythematosus, systemic sclerosis, relapsing polychondritis, vasculitis and atopic dermatitis. TCZ treatment in dermatology and adverse effects of the drug were reviewed here after the pharmacological properties, mechanism of action, dosage and administration of the drug were summarized. We estimate that by the help of newly well-designed studies with wider spectrum of subjects to comprehensively investigate the efficacy and safety will be able to contribute to the clinical management of the diseases especially refractory to the other treatments. Therefore, during the next decade, TCZ will be promising drugs in the treatment of refractory dermatological diseases.

Keywords

Alternative therapy, dermatology, tocilizumab

History

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Introduction

Interleukin 6 (IL-6) and IL-6 receptor were discovered by Tadimitsu Kishimoto at Osaka University in Japan in the 1980s. Tocilizumab (TCZ) is a recombinant-humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure. In 1997, 2001 and 2003 clinical studies for rheumatoid arthritis (RA), Castleman's disease and systemic juvenile idiopathic arthritis (SJIA) started, respectively. TCZ effectiveness for RA in combination therapy or as a monotherapy first reported in 2003^{1,2}. In further investigations, the effectiveness, tolerability and safety of TCZ in RA have been proven. In 2005, the first approval for the treatment of Castleman disease was taken in Japan. TCZ has been approved as a treatment for RA and SJIA since 2008. In 2010, it was approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe active RA. In 2011 and 2013, it was approved by FDA for the treatment of SJIA, polyarticular juvenile idiopathic arthritis (PJIA), respectively. TCZ has been used in limited dermatological diseases, however especially in the diseases that the IL-6 plays an important role in the pathogenesis, successful results have been reported with TCZ³. Below TCZ treatment in dermatology has been reviewed with the study reports after the pharmacological properties, mechanism of action, dosage and administration have been summarized.

Pharmacology

TCZ blocks IL-6-mediated signal transduction by inhibiting IL-6 binding to both transmembrane and soluble IL-6 receptors⁴. This complex binds to the 130 gp signal transducer and then the inflammatory cascade enhances, induces angiogenesis and amplifies the activity of adhesion molecules and the activation of osteoclasts⁵. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types, including T and B-cells, lymphocytes, monocytes and fibroblasts and has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA⁶. A concentration of free TCZ above 1 µg/mL in the serum enables the binding of 95% of the soluble IL-6 receptor inhibiting IL-6 actions and doubling the IL-6 serum levels after two weeks with intravenous application. Following subcutaneous (SC) dosing in RA patients, the absorption half-life was around 4 days. The half-life of TCZ is concentration dependent⁷.

In RA, the recommended dosage of TCZ for adult patients given as a 60 min single intravenous drip infusion is 4 mg per kg every four weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response. Doses exceeding 800 mg per infusion are not recommended. Subcutaneous form of TCZ regimen is weight dependent. Dose for patients less than 100 kg is 162 mg administered subcutaneously every

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other week, followed by an increase in every week based on clinical response. Dose for patients at or above 100 kg is 162 mg administered subcutaneously every week (PJIA), the recommended dosage of TCZ for PJIA patients given once every 4 weeks as a 60 min single intravenous drip infusion. Patients whose weight is less than 30 kg, recommended dose is 10 mg per kg and patients whose weight is at or above 30 kg, recommended dose is 8 mg per kg.

In SJIA, the recommended dose of TCZ for patients given once every two weeks as a 60 min single intravenous drip infusion. Patients whose weight is less than 30 kg, recommended dose is 12 mg per kg and patients whose weight is at or above 30 kg, recommended dose is 8 mg per kg³.

Dermatological usage

Psoriasis

IL-6 signaling pathway plays role in psoriasis pathogenesis as TNF- α , IL-23 and IL-17 signaling pathways. We have limited and contradictory data about effectiveness of TCZ in psoriasis. Its effectiveness was especially reported in pustular-type psoriasis and TNF- α -induced palmoplantar psoriasis^{8–11}. Paradoxically TCZ-induced psoriasiform dermatitis, exacerbation of pre-existing psoriasis and *de novo* psoriasis have also been reported^{12–16}. Because of the limited experience, it must be investigated in terms of the other signaling pathways.

Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Multiple cytokines play role in PsA pathological mechanism^{17,18}. PsA can be refractory to disease modifying antirheumatic drugs. New agents which acting on cytokines such as anti-TNF α , IL-1, IL-12/23, IL-17A and IL-6 have been developed¹⁹. TCZ treatment for PsA was recently tried but the efficacy was not favorable as in RA. Ogata et al. thought IL-6-dependent immune response activation may not be important in PsA²⁰. Only four cases have recently been published^{19,21,22}. In two cases, TCZ was found to be effective; one of the cases was refractory to conventional and other biological therapies and she became symptom-free with TCZ^{19,21}. Also, other two cases were reported whose arthritis and skin lesions were not improved despite six-month administration of TCZ²². However, since the data about this usage are unsatisfactory; it can be used in PsA when the disease is refractory to other treatments.

Behçet's disease

In Behçet's disease (BD), increased plasma IL-6 levels have a correlation with disease activity in the case of neurological involvement²³. Until now, eight BD cases who had improvement with TCZ have been reported^{24–29}. In all cases, TCZ dosage was 8 mg/kg every 4 weeks or 480 mg every 4 weeks. Hirano et al. reported that a BD patient who was successfully treated with TCZ as monotherapy²⁵. Addimanda et al. reported that three refractory neuro-Behçet patients who were treated with TCZ²⁷. One of them had a nearly complete response and the others had a partial response with TCZ.

Also, Urbaniak et al. and Shapiro et al. reported other neuro-Behçet patients who had good improvement²⁴. A case with pemphigus foliaceus and BD patient, who did not respond to corticosteroids, immunosuppressants, and biologic agents also had complete, long-lasting, clinical, and serological remission with TCZ²⁶. Another BD patient who had secondary amyloidosis, had also a complete remission and decreased proteinuria with colchicine and TCZ³⁰. Two mucocutaneous Behçet patients showed no response with TCZ and azathioprine combination²⁸. Also, paradoxical flares of mucocutaneous symptoms were reported in a BD patient after TCZ treatment. Cantarini et al. hypothesized blocking IL-6 might lead to worsening of the mucocutaneous lesions³¹. Hirano et al. have recently reported a case of a BD patient with severe posterior uveitis unresponsive to other therapies. TCZ monotherapy (8 mg/kg/month) resulted in the remission of the systemic manifestations with improvement of visual acuity and the frequency and severity of ocular attacks decreased²⁵. In refractory BD, especially in neurologic involvement, TCZ may be a therapeutic option.

Systemic lupus erythematosus

The pathogenesis of systemic lupus erythematosus (SLE) involves multiple components of the immune system, including B cells, T cells, cytokines and growth factors. TCZ decreases lymphocyte activation and restores B and T cell homeostasis by either blocking differentiation and/or trafficking in patients with SLE³². Serum IL-6 levels, urinary excretion and renal expression of IL-6 and IL-6 levels in cerebrospinal fluid are elevated in SLE patients. So TCZ can prevent onset and progression of the disease³³. The dosage of the TCZ used in SLE is 2 mg/kg or 4 mg/kg or 8 mg/kg bi-weekly. Illei et al. reported that 16 SLE patients treated with TCZ; significant improvement in the modified Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index score was observed in 8 of the 15 evaluable patients³⁴. Arthritis improved in all arthritic patients and anti-dsDNA antibody levels decreased. Adverse effects included a dose-related decrease in the absolute neutrophil count that normalized after cessation of treatment. Infections occurred in 11 patients but were not associated with neutropenia³⁴. TCZ was reported successfully in refractory massive pericardial effusion and refractory hemolytic anemia due to lupus pericarditis^{35,36}. TCZ was also found to be effective in the cutaneous manifestations of SLE; a refractory SLE patient with fever, arthritis, diffuse rash with urticarial vasculitis and tumid lupus which did not respond to other therapies, had totally improvement with TCZ³⁷. Therefore, it can be concluded that TCZ can be beneficial in refractory SLE.

Systemic sclerosis

Patients with systemic sclerosis (SSc) have elevated IL-6 levels in blood mononuclear cells and soft tissue culture supernatants^{38,39}. Furthermore, IL-6 increasement degree was found to be dependent on the skin thickness score⁴⁰. Shima et al. reported that two SSc patients who had diffuse skin disease and treated with once monthly infusions of TCZ at

8 mg/kg for duration of six months. After TCZ treatment, both patients showed softening of the skin and histological examinations revealed thinning of the collagen fiber bundles in the dermis⁴¹. Another two SSc patients who were administered TCZ for six months showed a decrease in their modified Rodnan total skin scores, suggesting that their skin sclerosis could have been improved with TCZ⁴². Also, TCZ was found to be effective in SSc polyarthritis and SSc-myopathy⁴³. Currently, a Phase II/III multicenter randomized, double-blind placebo-controlled trial is underway to assess the safety and efficacy of TCZ in early active skin disease in SSc⁴⁴.

Relapsing polychondritis

Seven relapsing polychondritis (RPC) cases have been reported until now^{45–49}. Two of them were refractory RPC complicated with aortitis were successfully treated with TCZ^{45,49}. In four case reports, complicated with laryngo-tracheal involvement was successfully treated^{45,47,49,50}. Eight milligrams per kilogram a monthly TCZ treatment had been applied. All cases were refractory to conventional treatment. Therefore, TCZ can be considered as a therapeutic option in RPC patients who have failed anti-TNF therapy.

Adult onset Still's disease

In adult onset Still's disease (AOSD), elevated levels of IL-6 and other proinflammatory cytokines have been demonstrated. IL-6 has been associated with systemic symptoms such as fever and skin rash and correlated with raised serum CRP, ferritin and leukocytes levels, as well as with disease activity⁵¹. In a multicenter retrospective open-label study; 34 AOSD patients who had refractory to other therapies were treated with TCZ. The initial dosages of intravenous TCZ were 8 mg/kg every 4 weeks in 22 patients, 4 mg/kg every 4 weeks in 2 patients and 8 mg/kg every 2 weeks in 10 patients. Rapid and maintained improvement in both clinical and laboratory parameters were achieved. The median dosage of prednisone was also reduced. Only two patients discontinued the therapy because of the severe infections⁵². Besides a lot of case reports and case series have been reported about the TCZ use in AOSD^{53,54}. They all had improvement with TCZ. However, joint manifestations seem to be more refractory to treatment when comparing with systemic manifestations^{52,54}. There is no consensus about the dosage. Higher dosage is advised whose disease is very active⁵². It has a significant corticosteroid-sparing effect. Furthermore, IL-1 and IL-6 inhibitors seem to be more efficient than TNF-alpha inhibitors⁵⁵.

Vasculitis

TCZ is particularly effective in large vessel vasculitis; Takayasu arteritis (TA) and giant cell vasculitis (GCV)^{56–58}. It has been shown that IL-6 plays an important role in the pathogenesis of GCV and TA. TA patients who were especially refractory to other conventional, immunosuppressive and other biological therapies, achieved good clinical response and rapid normalization of the acute phase proteins and some of them had significant reduction in thickened

arterial lesions^{59–64}. TCZ therapy (4 mg/kg, 8 mg/kg monthly) was effective and well tolerated in TA. A three-year-old girl with TA also had a rapid clinical remission with TCZ infusions (8 mg/kg for two weeks)⁶⁵. In GCV, especially relapsing or refractory to other treatments, clinical and laboratory and radiological improvement was achieved with TCZ (4 mg/kg or 8 mg/kg)^{66–70}. Emerging reports on the use of TCZ suggest an important role of IL-6 in the pathogenesis of large-vessel vasculitis, however further investigations are needed⁵⁷. TCZ was also reported to be effective in rituximab-refractory cryoglobulinemia vasculitis, a case with urticarial vasculitis and refractory cutaneous lupus and systemic rheumatoid vasculitis^{37,71,72}.

Graft versus host disease

An important role of IL-6 in the severity of acute graft versus host disease (GVHD) was demonstrated⁷³. Drobyski et al. reported that 8 steroid refractory GVHD patients (6 acute GVHD and 2 chronic GVHD) who were treated with TCZ once every 3–4 weeks. Four patients with acute GVHD had partial or complete responses. One patient with chronic GVHD had a significant response to therapy, whereas the second had only stabilization of disease. TCZ also had some efficacy in the treatment of skin sclerosis⁷⁴. Also, a three-year-old boy who had bone marrow transplant because of sickle cell disease developed grade III acute graft versus host disease of the gut, which was refractory to methylprednisolone and other treatments. He had remission with TCZ⁷⁵. Therefore, it can be concluded that TCZ may be effective in the treatment of steroid refractory GVHD.

Usage in other diseases

Atopic dermatitis

Three atopic dermatitis patients to phototherapy, topical steroids, calcineurin inhibitors and in two cases refractory to oral cyclosporine had more than 50% improvement with TCZ (8 mg/kg monthly) within three months. However, two of them developed bacterial infection⁷⁶. Therefore, TCZ may decrease the clinical activity of atopic dermatitis but can be associated with bacterial superinfection.

Overlap syndrome

A patient with concomitant dermatomyositis (DM), SSc and RA had a good response with TCZ treatment, therefore it can be concluded that it was effective not only for RA but also for DM and SSc⁷⁷.

Pemphigus foliaceus

A case of a woman affected with pemphigus foliaceus and Behçet disease, who did not respond to corticosteroids, immunosuppressants and biologic agents, including adalimumab, anakinra or infliximab had a complete, long-lasting, clinical and serological remission with TCZ monotherapy²⁶. So it may be beneficial in autoimmune bullous disease like pemphigus foliaceus.

FDA approved and dermatological usage of TCZ has been summarized in Table 1.

Table 1. TCZ usage.

FDA approved usage
RA
Systemic juvenile idiopathic arthritis
PJIA
Dermatological usage
Psoriasis
Psoriatic arthritis
BD
Systemic lupus eritematosus
Systemic sclerosis
Relapsing polychondritis
Adult onset Still's disease
Vasculitis
TA
GCV
GVHD
Atopic dermatitis
Overlap syndrome
Pemphigus foliaceus

Adverse effects

Infections

TCZ can cause serious infections, including tuberculosis, bacterial, invasive fungal, viral and other opportunistic infections like the other biological agents. The most commonly reported infections were upper respiratory tract infections and nasopharyngitis^{78,79}. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis^{78,80–86}. Cases of opportunistic infections such as tuberculosis, *Cryptococcus*, aspergillosis, candidiasis, and pneumocystosis have also been reported⁸⁷.

Gastrointestinal perforation

Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess^{88,89}. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications, corticosteroids or methotrexate. The relative contribution of these concomitant medications versus TCZ-IV to the development of GI perforations is not known. Besides, gastrointestinal ulcers, severe hepatitis have been reported^{90–92}.

Laboratory parameters

Treatment with TCZ was associated with laboratory parameters changes. In controlled trials, neutropenia $<2000/\text{mm}^3$ have been reported 16–39% of patients receiving TCZ 8 mg/kg. Most of them were mild and occurred within eight weeks of therapy. Infections have been uncommonly reported in association with treatment-related neutropenia^{92–96}. In controlled clinical studies, decreases in the platelet counts below 100 000 per mm^3 occurred in 1.3%, 1.7% and 0.5% of patients on intravenous 4 mg per kg and 8 mg per kg and placebo groups, respectively, without associated bleeding events. In subcutaneous group, none of the patients had a decrease in platelet count to $\leq 50 \times 10^3/\text{mL}$ ^{92,96}.

Treatment with TCZ was also associated with a higher incidence of transaminase elevations. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant drug, interruption or reduction of TCZ resulted in decrease or normalization of liver enzymes^{2,91,94,96–98}. Elevations of the lipid parameters (total cholesterol, LDL, HDL and triglycerides) were seen at 6th week of TCZ treatment and remained stable thereafter in 24th week clinical trials. Increases in triglycerides levels as above 500 mg per dL were rarely observed and elevated lipids responded to lipid lowering agents^{92,96}.

Immunosuppression and malignancies

Malignancies were observed in clinical studies of TCZ. The impact of the TCZ on the development of the malignancies is not known, but TCZ is an immunosuppressant so may increase the risk of malignancies. Hematologic/lymphatic malignancies, solid cancers and non-melanoma-skin cancers have been reported^{94,95,99}.

Infusion and injection site reactions

The most frequently reported event during the infusion was hypertension. After infusion within 24 h, the most frequently reported events were headache and skin reactions such as rash, pruritus and urticaria. At the injection site erythema, pruritus, pain and hematoma can be observed in a mild to moderate severity and mostly resolved without any treatment^{94,100,101}.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, with or without a fatal outcome have been reported with intravenous infusion. These reactions were generally observed during the second to fourth infusion of TCZ. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction^{92,95,101,102}.

Demyelinating disorders

The impact of TCZ on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies^{95,96,103}.

Immunogenicity

Anti-TCZ antibodies can develop during the TCZ treatment. In controlled studies, 2% of the patients who had intravenous TCZ treatment developed positive anti-TCZ antibodies, and some of them had medically significant, hypersensitivity reaction leading to withdrawal. In subcutaneous group, 0.9% developed anti-TCZ antibodies^{104–106}.

The adverse effects of TCZ have been summarized in Table 2.

Drug interaction

TCZ has the potential to affect expression of multiple CYP enzymes, including CYP450, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. TCZ leads to increased

Table 2. Adverse effects of TCZ.

Infections
Upper respiratory tract infections
Nasopharyngitis
Pneumonia
Urinary tract infection
Cellulitis
Herpes Zoster
Gastroenteritis
Diverticulitis
Sepsis
Bacterial arthritis
Tuberculosis
Cryptococcus
Aspergillosis
Candidiasis
Pneumocystosis
Gastrointestinal disorders
Abdominal pain
Mouth ulceration
Gastritis
Gastrointestinal ulcers
Severe Hepatitis
Laboratory parameters
Elevated hepatic transaminases leukopenia
Neutropenia
Hypercholesterolemia
Hypertriglyceridemia
Hyperbilirubinemia
Skin and subcutaneous tissue disorders
Rash
Pruritus
Urticaria
Ulcer
Psoriasis
Vascular disorders
Hypertension
Nervous system disorders
Headache
Dizziness
Demyelinating disorder
Leukoencephalopathy

metabolism of drugs that are substrates of them. The effect of TCZ on CYP450 enzyme activity may persist for several weeks after stopping therapy^{94,96,107,108}.

Warnings and precautions

TCZ is contraindicated in the case of hypersensitivity to TCZ and severe uncontrolled infections such as sepsis or opportunistic infections and in patients with an active infection, including localized infections. This drug should be used with caution in patients who may be at increased risk for gastrointestinal perforation. TCZ is not recommended in patients with a low neutrophil count before treatment and who develop an absolute neutrophil count less than 500 per mm³; a platelet count below 100 000 per mm³ before treatment and who develop a platelet count less than 50 000 per mm³, elevated transaminases greater than 1.5× upper limit of normal levels before treatment and who develop elevated ALT or AST greater than 5× upper limit of normal levels. Neutrophil, platelet counts, ALT and AST levels, lipid parameters should be monitored 4–8 weeks after the

beginning of the therapy and every 3 months. Serological tests for hepatitis B and C should be done at the beginning of the therapy. TCZ is also not recommended in patients with active hepatic disease or hepatic impairment. Usage of live vaccines concurrently with TCZ should be avoided as clinical safety has not been established. Besides patients should be monitored for signs and symptoms of demyelinating disorders and malignancies. Pregnancy category of TCZ is category C¹⁰⁹. Because of the TCZ elimination, half-life suggests three months, conception is recommended three months after the last infusion for both genders. TCZ is also present in human milk or if it would be absorbed systemically in a breastfed infant after ingestion³.

Future direction

During the next decade TCZ will be widely used especially for the refractory various diseases. Therefore, further well-designed studies with wider spectrum of subjects will be required to comprehensively investigate the efficacy and safety that will be able to contribute to the clinical management of the diseases especially refractory to the other treatments.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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