

# Treatment of Connective Tissue Disease-Related Intractable Disease with Biological Therapeutics

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**Abstract:** The treatment of connective tissue disease (CTD) and CTD-related intractable diseases (CTD-IDs) currently depends on the use of steroid therapy. Approximately 20 years have passed since the approval of infliximab for rheumatoid arthritis in 2003. Since then, several biological therapeutics have been marketed and adapted for many CTDs and CTD-IDs other than rheumatoid arthritis. Although conventional treatment for patients with these diseases is rarely used because of their poor prognosis, these cases may benefit from biological therapeutics. However, choosing biological therapeutics is difficult because they have different target molecules compared with conventional therapeutics. In this review, we address the current situation of biological therapeutics for CTD-IDs including Behcet's disease, psoriatic arthritis, ankylosing spondylitis, anti-neutrophil cytoplasmic antibody-related arthritis, and adult Still's disease, as well as the choice of biological therapeutics in clinical practice.

**Keywords:** connective tissue disease-related intractable disease, biological therapeutics, clinical practice, inflammatory cytokine

## Introduction

Connective tissue disease (CTD) is a histopathological concept proposed by the American pathologist Paul Klemperer in 1942.<sup>1</sup> It is used to describe acute or chronic diseases characterized by abnormalities including diffuse denaturation of the connective tissue (dermis, ligament, tendon, bone, cartilage), particularly extracellular components, such as collagen. Currently, six diseases including rheumatic fever, rheumatoid arthritis (RA), polyarteritis nodosa, systemic lupus erythematosus, systemic scleroderma and dermatomyositis are termed "classic CTDs".<sup>2,3</sup> CTD is a clinical diagnosis term for a single disease group with similar histopathological characteristic but not similar etiologies or genetics.<sup>4-6</sup> In the current classification, several CTD-related intractable-disease (CTD-IDs) other than "classic CTDs" have been proposed including polymyositis, mixed CTD, Sjogren's syndrome, vasculitis syndrome, juvenile idiopathic arthritis, adult Still's disease (ASD), Behcet's disease (BD), and anti-phospholipid syndrome.<sup>7-9</sup>

Biological therapeutics are commonly used for the treatment of immunological disease and malignancy, because they are high effective compared with conventional treatments using small molecules.<sup>10</sup> High polymer preparations, termed biological therapeutics, which block cytokines are used to treat CTD and rheumatic disease whereas molecules targets are required for the treatment of malignant tumor.<sup>10</sup> First, rituximab was approved for the treatment of malignant lymphoma, resulting in

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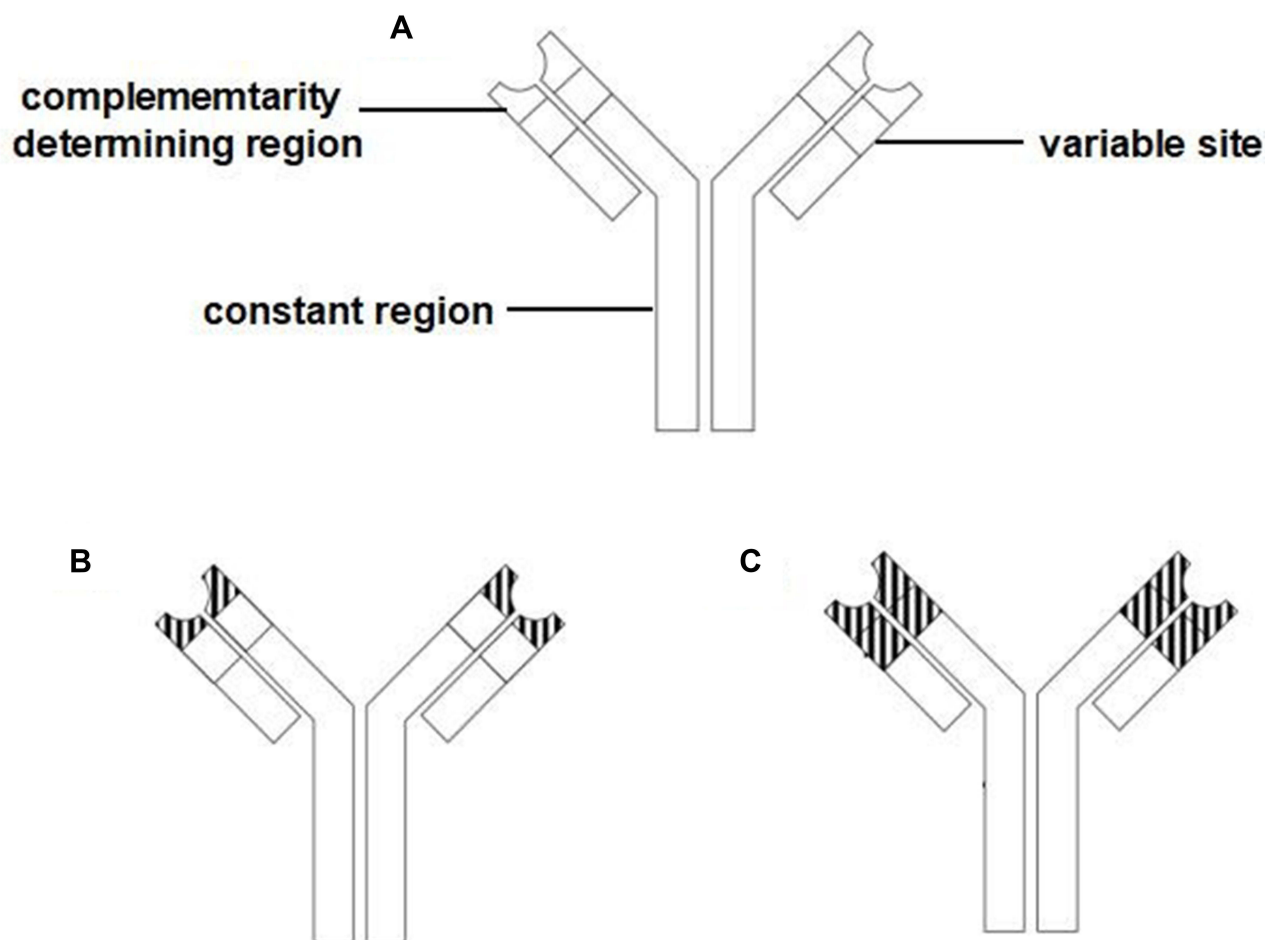
a breakthrough for blood disorders.<sup>11</sup> Infliximab has been used to treat Crohn's disease and RA.<sup>12</sup> Researchers predicted RA symptoms could be improved by blocking inflammatory cytokines such as tumor necrosis factor (TNF) $\alpha$ , interleukin (IL)-6 and IL-1 $\beta$ , because these cytokines were strongly related to the pathophysiology in RA. Then, biological therapeutics for BD, vasculitis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and systemic lupus erythematosus were developed and recommended by medical treatment guidelines for the treatment of each disease.<sup>13–16</sup>

In the field of medicine, biological therapeutics consist of proteins as well as insulin, immunoglobulin (Ig) preparations, and vaccines. However, in the field of CTD and CTD-ID, biological therapeutics describe drugs that inhibit the production or function of cytokines or kill specific lymphocyte populations. Biological therapeutics include monoclonal antibodies and protein fusion preparation (receptor molecules). In general, monoclonal antibodies destroy cytokine- or antibody-

producing cells by the binding to a cell surface receptor or target antigen. Receptor molecules, also called decoy molecules, are fused to a receptor that binds to IgG, which prevents the binding of the target (eg, cytokine) to its receptor.<sup>17</sup> The first monoclonal antibody preparations were from mice, but their immunogenicity prevented their long-term use for clinical applications. To reduce immunogenicity, chimeric model antibodies, humanized antibodies, and human antibodies were developed. Human antibodies encoded by human antibody gene contain no mouse molecules (Figure 1). In this review, we discuss the current situation of biological therapeutics for CTD-IDs including BD, PsA, AS, anti-neutrophil cytoplasmic antibody (ANCA)-related arthritis, and ASD, as well as the choice of biological therapeutics for clinical practice.

## Behcet's Disease (BD)

BD is characterized by inflammation of the skin, mucous membranes, and uvea.<sup>18</sup> Uveitis, particularly posterior uveitis,



**Figure 1** Three types of therapeutic immunoglobulins. (A) Human antibody; (B) Humanized antibody; (C) Chimeric model antibody. Immunoglobulins consist of a complementarity determining region, variable site, and constant region.

rarely causes altitude inflammation, which leads to blindness.<sup>8,18</sup> Intestinal, vascular, and nervous BD often affect the disease prognosis.<sup>18</sup> The pathogenesis of BD is related to TNF $\alpha$ .<sup>19</sup> T cells in BD patients respond to a small amount of staphylococcal exotoxins and produce cytokines.<sup>20</sup> Two anti-TNF $\alpha$  monoclonal antibodies (infliximab and adalimumab) have been adapted for BD treatment and infliximab has been approved for all types of BD. It is necessary to administer a combination therapy of methotrexate (MTX) and infliximab in RA patients because of the influence of anti-infliximab antibody production. However, this combination with MTX is unnecessary in BD patients. Furthermore, the addition of MTX does not provide benefit compared with infliximab treatment alone. However, when an immunosuppressant was used with adalimumab it was reported that “there might be the clearance drop of adalimumab by combination with MTX and uses it together and warns us”. The frequency of uveitis is related to blindness. Therefore, for the treatment of BD uveitis, it is important to control eye inflammation. The whole-body dosage of glucocorticoids improves symptoms related to BD, but the long-term control of BD is unknown. Oral immunized suppressants to treat uveitis have been superseded by infliximab. The 2018 EULAR Recommendations for BD indicate infliximab as a first-choice treatment for ophthalmitis although there is concern regarding its functional decline over time.<sup>21</sup> Adalimumab is not approved for BD uveitis because no related clinical studies were initiated at the time of development.<sup>22,23</sup> However, some studies have reported adalimumab suppressed uveitis in BD.<sup>24,25</sup>

## Intestinal Type BD

Intestinal type BD often forms an ulcer in the ileocecum as well as the gastrointestinal tract but rarely causes perforation. It accounts for 15–20% of all BD cases and usually requires surgery. Intestinal type BD is treated with GCs and 5-aminosalicylic acid or salazosulfasalazine according to the therapeutic guidelines for inflammatory bowel disease. However, the long-term use GC causes complications including perforation caused by a delay in wound healing. Infliximab and adalimumab are effective in patients who are resistant to GCs and 5-aminosalicylic acid or salazosulfasalazine.<sup>26–28</sup> In addition, adalimumab and infliximab were highly effective in clinical trials of cases with a typical ulcer 1 cm in diameter in the ileocecum where GCs or immunosuppressants were not effective part.<sup>26,29</sup> However, TNF inhibitor treatment is unsuccessful in approximately 20% of patients.

## Nervous Type BD

Nervous type BD can be classified as an acute model/ANB (acute neurological attacks in BD) and chronic progressive/CPNB (chronic progressive neurological BD). Both types require treatment because they reduce the quality of life for patients. Infliximab has been used in a model of nervous BD, but evidence is lacking for its use in multi-cases. Conventional treatment consisting of GCs and pulse therapy is used for the induction of remission in ANB. However, the effects of infliximab on attack prevention have only been reported for backward cohorts and cases.<sup>30</sup> MTX generally improved convalescence in CPN,<sup>31</sup> and infliximab was effective in cases where MTX was ineffective.<sup>32</sup>

## Vascular Type BD

Vascular type BD describes numerous diseases that can develop in a single patient related to lesions of the vein and artery system. Genuine and false aneurysms appear in arteries and clot formation occurs in veins. The symptoms of vascular type BD are likely to be worsened by stimulation, similar to intestinal tract type BD. In addition, in this type BD, false aneurysms occur in blood vessel anastomotic regions after aneurysms are substituted with artificial blood vessels, making it difficult to treat. The use of glucocorticoids or immunosuppressants for vascular lesions in BD has been recommended by EULAR, although robust evidence for their effects is lacking.<sup>33,34</sup> Anti-TNF preparations (infliximab and adalimumab) were reported to be effective in cases resistant to glucocorticoids or immunosuppressants.<sup>35,36</sup> Anti-TNF preparations are often used in intractable cases and those requiring surgical management, such as those with intestinal tract type BD. Discontinuation studies in RA and the dosage period of biological therapeutics have been reported, but there is no clear evidence for discontinuation in BD. However, remission was maintained without uveitis for one year even when substitute treatments, such as immunosuppressants were used in cases that could not continue infliximab.<sup>37</sup>

## Psoriatic Arthritis (PsA)

PsA is broadly classified as a form of vertebral pain (spondyloarthritis: SpA). There is often a “peripheral phenotype” in which patients’ symptoms mainly comprise synovium inflammation similar to that in RA. However, some cases exhibit “body axis characteristics” symptoms, and these cases are difficult to identify with AS in X-ray

views. In addition, dactylitis that shows enthesitis and swelling in all fingers and toes has various joint symptoms. Body axis-related joint symptom is stronger in inflammation of the ligament than in synovium, and hardening lesions resulting from the ossification of the ligament is the primary problem, rather than bone destruction. Body axis-related joint lesions were reported in 25–70% of cases.<sup>38</sup> It is important to know which cytokines are related to joint symptoms because the recommended drugs differ for peripheral joint pain, body axis-related joint pain, enthesitis, and dactylitis in PsA.<sup>39,40</sup>

It was previously reported that cyclosporine was effective for treating skin lesions in patients with psoriasis when psoriasis patient incorporated the examination to check the effectiveness of cyclosporine for RA.<sup>41</sup> Another report suggested that T cell-related immunity (T helper (Th)1 reactions) participated in the skin symptom of psoriasis patient. Then, IL-17 and IL-22 were shown to be involved in psoriasis lesions, indicating Th17 cells were also involved.<sup>42,43</sup> IL-12 produced by dendritic cells is important for the differentiation of Th1. In addition, IL-23 produced by dendritic cells increases and maintains IL-17 cells. IL-12 and IL-23 form a heterodimer comprising a subunit of p35/p40 and p19/p40, respectively. p40 is the subunit common to IL-12 and IL-23. The expression of p40, but not p35, was increased in the skin lesions of psoriasis patients,<sup>44</sup> and IL-17 and IL-22 (Th17-related molecules) in psoriasis skin lesions were related to treatments, such as etanercept and cyclosporine.<sup>40,45</sup> In addition, psoriasis-like exanthem and expression of IL-17A occurred when IL-23 was injected to the skin of mice.<sup>46</sup> It is thought that Th17 cells contribute more significantly to skin lesion compared with Th1 cells. As for TNF $\alpha$ , it turns out that it is involved in the condition of patients' dendritic cells, Th17, and epidermal cornification cells, both situations broadly. Although PsA exhibits various joint symptoms, the cytokines involved might vary according to the symptoms. The participation of TNF $\alpha$  is strongly suggested in peripheral arthritis, because TNF inhibitors suppressed inflammation in peripheral joint pain in RA and prevent joint destruction. However, local cells in tissues produce IL-23, IL-17 and

IL-22, which might participate in enthesitis.<sup>47,48</sup> Previous studies reported enthesitis was IL-17A-dependent in animal models.<sup>47,49</sup> Enthesitis might have a similar cytokine profile to skin lesions in psoriasis, because  $\gamma \delta$  T cells in the human vertebral column spinous process produce IL-17A by an IL-23-independent mechanism.<sup>50</sup>

The priority of biological therapeutics for the treatment of joint symptoms of PsA is shown in Table 1. TNF inhibitors have the best efficacy against peripheral joint pain. The IL-17A inhibitor has a superior effect to the IL-12/23p40 inhibitor, but similar efficacy to TNF inhibitor.<sup>51–53</sup> However, the effects of brodalumab, an IL-17 receptor A inhibitor, on preventing joint destruction are unclear.<sup>54</sup> In addition, guselkumab, an IL-12/23p19 inhibitor, is superior to IL-12/23p40 inhibitors for the improvement of clinical joint, and has similar efficacy to TNF inhibitors and the IL-17 inhibitor.<sup>55</sup> Although the benefit of IL-12/23p40 for peripheral joint pain is unclear, improvements in joint pain and joint destruction were significant compared with placebo in a clinical study.<sup>56,57</sup> In addition, an IL-12/23p40 inhibitor significantly improved enthesitis compared with a TNF inhibitor,<sup>58</sup> and had benefit for dactylitis. In addition, a high percentage of cases continue ustekinumab treatment because it has very low accumulation rate, which reduces the potential for harmful phenomena.<sup>58</sup> TNF inhibitors and anti-IL-17 biological therapeutics are considered first choice for the treatment of axis-related joint pain. The EULAR recommendations suggest TNF inhibitors are the first choice for treatment, but IL-17A inhibitors are also recommended as first choice in some cases.<sup>59</sup> IL-17A inhibitors were superior regarding the rapidity of effect and reducing disease severity in psoriasis exanthem, similar to TNF inhibitors. However, IL-17A inhibitors should be used with caution for inflammatory bowel disease, because IL-17A is necessary for maintenance of the enterobacterial flora.

# Ankylosing Spondylitis (AS)

AS, a chronic inflammatory disease that develops at a young age, is characterized by ankylosis observed in sacroiliac joint by imaging. Furthermore, lesions occur

**Table 1** Priority of Biological Therapeutics for the Treatment of Joint Symptoms of PsA

Pattern of Arthritis	Priority of Biological Therapeutics
Peripheral Arthritis	TNF $\alpha$ inhibitor $\approx$ IL-17 inhibitor $\approx$ p19 > p40 inhibitor
Axial Spondyloarthritis	TNF $\alpha$ inhibitor $\approx$ IL-17 inhibitor > p40 inhibitor
Adhesive Inflammation	p40 inhibitor $\geq$ TNF $\alpha$ inhibitor $\approx$ IL-17 inhibitor
Dactylitis	p40 inhibitor $\geq$ TNF $\alpha$ inhibitor $\approx$ IL-17 inhibitor

along the vertebral column from the upper part to the lower part, finally causing total ankylosis of the vertebral column. The classification standard (revision New York standard) comprises clinical and X-ray imaging.<sup>60</sup> Without a specific spot that meets the criteria of “more than grade 3 on one side and more than grade 2 on both sides” in sacroiliac joint with X-rays, we cannot make a diagnostic decision. This was the classification standard in 1984 and only non-steroidal anti-inflammatory drugs (NSAID) were available, which did not alter the disease course.<sup>60</sup> Currently, TNF inhibitors are administered, which markedly improve symptoms leading to an early cure. The Assessment of Spondyloarthritis International Society (ASAS) classified axial spondyloarthritis (axSpA) in 2009.<sup>61</sup> Although the main disease of this classification is AS, it includes axSpA, which is not present in the revised New York standard of AS. Actually, axSpA, which meets the x-ray standard, almost matches AS according to the revised New York standard.<sup>62</sup> However, non-axSpA does not necessary occur in early AS.<sup>63,64</sup> AS is characterized by negative CRP, and non-axSpA tends to have negative or low CRP values. Therefore, inflammation assessed by magnetic resonance imaging is likely to be low.<sup>65</sup> Because the ASAS standard includes diseases other than AS, we should carefully consider the diagnosis. However, the ASAS standard is very useful for the diagnosis of AS.

TNF $\alpha$ , IL-17A and IL-23 are increased in patient with AS.<sup>66–68</sup> It is thought that TNF $\alpha$  is important at the final stage of inflammation, and many studies have reported that TNF inhibitors are effective for AS. It is thought that IL-17A participates in the maintenance of chronic inflammation related to TNF $\alpha$  receptor signaling and IL-23 participates in the differentiation and IL-17 production of Th17 cells.<sup>69</sup> TNF inhibitors and IL-17 inhibitors are effective in AS. However, when AS was treated with TNF inhibitors, serum IL-17A levels unchanged regardless of the treatment effect.<sup>70,71</sup> Therefore, IL-17 inhibitors might be used for patients who derive no benefit from TNF inhibitors.<sup>72</sup> In addition, IL-17 inhibitors have similar efficacy to TNF inhibitors in active AS patients without biological therapeutics.<sup>73</sup> These results suggest IL-17A participates uniquely in the pathophysiology of AS. Although IL-23/p19 or IL-23/p40 inhibitors did not show a statistically significant improvement, they were effective in patients with AS.<sup>74,75</sup> From this, although PsA and AS are related diseases, the role of IL23 in enthesitis is different between these diseases.

MTX has not been confirmed for sacroiliac joint and the vertebral column, the central lesions in AS and non-axSpA. Salazosulfasalazine is validated only for peripheral joints when accompanied by peripheral joint pain.<sup>76</sup> Therefore, TNF inhibitors or IL-17 inhibitors are used when NSAIDs can be used and BASDAI score is greater than 4. Recommendations by ACR, Spondylitis Association of America (SAA) and Spondyloarthritis Research and Treatment Network (SPARTAN) were updated in 2019.<sup>77</sup> The first-line drug is usually a TNF inhibitor. Uveitis in the front of the eye is detected in about 1/3 of AS cases. Therefore, in such cases, TNF inhibitors should be given priority. TNF and IL-17 inhibitors are highly effective when lesions are evaluated clinically by BASDAI, but their effects on suppressing bone lesion progress are unclear. This is because no system to evaluate bone lesions in AS patients has been established compared with RA and PsA patients. However, the possibility has been suggested that TNF inhibitor and IL-17 inhibitor allow for gentle and quiet long-term incorruptibility.<sup>78</sup> In addition, one report indicated the possibility that bone deterioration was inhibited after 2 years of secukinumab treatment.<sup>79</sup> Therefore, we anticipate the results of analyses of other examples of this treatment over longer periods. At present, it is not recommended to discontinue or reduce TNF inhibitors or IL-17 inhibitor use, even if disease activity has slowed according to evaluations such as BASDAI.

## Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Related Arthritis

Vasculitis syndrome is classified according to the size of affected blood vessel by the Chapel Hill Consensus Conference (CHCC) classification (CHCC, 2012).<sup>80</sup> The classification of small vasculitis in CHCC 2012 are an immune complex type and an ANCA-related vasculitis type. The former type comprises anti-glomerular basement membrane antibody disease, IgA vasculitis, and cryoglobulinemia-related vasculitis. ANCA-related vasculitis includes microscopic polyangiitis (MPA), polyangiitis-related granulation tissue class symptom (granulomatosis with polyangiitis (GPA) or Wegener granulomatosis), and eosinophil- and polyangiitis-related granulation tissue class symptom (eosinophilic granulomatosis with polyangiitis (EGPA), Churg-Strauss syndrome, or allergic granulomatous vasculitis).<sup>80</sup> MPA and GPA require similar therapeutic strategies although they are different diseases.



The pathogenesis of MPA and GPA is thought to involve neutrophil extracellular traps (NETs) released from ANCA-activating neutrophil, which affect endothelial cells via inflammatory cytokines.<sup>81,82</sup> EGPA is different from MPA and GPA because it is an eosinophil-related tissue disorder. In EGPA, Th1/17 cells participate in granuloma formation, TRh2 produce IL-4, IL-5, and IL-13, and B cells secrete IgE and ANCA. IL-5 activates eosinophil, which causes the tissue disorder. Anti-IL-5 biological therapeutics is used for the treatment of EGPA and anti-B-cell therapy is used for MPA and GPA.

Rituximab is a monoclonal antibody that recognizes CD20 expressed on the surface of B-cells. After binding to CD20, rituximab kills B-cells by antibody-dependent cellular cytotoxicity. Rituximab is covered by health insurance for the treatment of MPA and GPA in Europe and the USA.<sup>83–85</sup> However, GCs plus rituximab is positioned as an alternative to GCs plus cyclophosphamide treatment for MPA and GPA. In MPA and GPA, rapidly progressive glomerulonephritis is often complicated as an organ disorder, and clinicians often hesitate to use GCs plus rituximab because cyclophosphamide used in standard regimen can affect liver function test outcomes. However, because there is no need for weight loss, and rituximab used in limited quantities does not cause renal failure, there are many clinical situations where its use is appropriate.

Mepolizumab, a monoclonal antibody that recognizes IL-5, is covered by health insurance for the treatment of severe bronchial asthma. This drug has a strong eosinophilic suppressive effect mediated by IL-5 inhibition and is covered by health insurance for the treatment of EGPA.<sup>86</sup> GCs are a first-line drug for the treatment of EGPA, but not MPA and GPA, because not many cases require immunosuppression in the early stages of disease. Mepolizumab can achieve rapid drug weight loss of GCs compared with placebo and can achieve longer-term remission maintenance.<sup>86</sup> The use of mepolizumab is considered in cases where the use of GCs or immunosuppressants is difficult because of the occurrence of side effects.

## Adult Still's Disease (ASD)

ASD is not an autoimmune disease because it lacks auto-reactive T-cells and autoantibodies. Its pathogenesis involves the activation of monocytes/macrophages and the production of inflammatory cytokines. Therefore, ASD is classified as a CTD-ID, but it is considered an autoinflammatory disease.<sup>87</sup> IL-6, IL-18, and TNF $\alpha$  are present at high levels in patients with ASD, although many cytokines have been reported.<sup>87,88</sup> The characteristics of ASD include high levels

of ferritin and IL-18. In ASD, increased IL-18 is related to fever, joint pain, and skin symptoms, which are normalized by GC treatment.<sup>89</sup> In addition, IL-6 located downstream to IL-18 might be increased or decreased in ASD.<sup>90</sup>

Regarding biological therapeutics for ASD, TNF $\alpha$ , IL-1, and IL-6 inhibitors have shown benefit. A meta-analysis of clinical studies reported the IL-1 inhibitor, anakinra, improved the remission rate and GC-induced weight loss.<sup>91</sup> In addition, another IL-1 inhibitor, canakinumab, improved juvenile idiopathic arthritis similar to ASD in a clinical trial.<sup>92</sup> A TNF inhibitor was also effective for ASD in a forward open clinical study.<sup>93</sup> Furthermore, Kaneko et al<sup>94</sup> reported that tocilizumab had a high remission rate for ASD compared with placebo in a double-blind study. Based on these studies, tocilizumab was approved for ASD.

The condition of patients requiring a prescription of life convalescence of ASD includes macrophage activation syndrome (MAS). MAS defines the prognosis of ASD. Although there is no specific treatment for ASD, an adaptation of tocilizumab treatment can cause MAS. It is assumed that MAS develops in patients where “ASD that the effect is insufficient by existing treatment”, which is an adaptation of tocilizumab. Therefore, it is necessary to consider MAS development after tocilizumab treatment or the use of TNF $\alpha$  or IL-1 inhibitors.<sup>95–97</sup> However, it is reported that a clear cause-effect between the tocilizumab dosage and MAS onset could not be found from the results of analyzed cases which MAS developed after administration of tocilizumab for juvenile idiopathic arthritis resembling ASD.<sup>98</sup> Pathology resembling cytokine storm might cause MAS. Therefore, biological therapeutics might cause changes in the cytokine cascade and trigger MAS onset. Therefore, it is necessary to consider the usefulness of tocilizumab against ASD patient developing MAS.

## Combination Therapy Using Biological Therapeutics

The cost of biological therapeutics per patient with RA is approximately 100 times the costs of treatment with a combination of conventional disease-modifying antirheumatic drugs (DMARD). Graudal et al<sup>99</sup> reported a meta-analysis of randomized trials of combination therapy with and without TNF inhibitors in RA. They concluded the RA guidelines should recommend combination treatment before the initiation of TNF inhibitors. The effect of combination therapy including biological therapeutics was also reported in patients with CTD-ID.<sup>100,101</sup>

AS is a chronic and inflammatory disease, and the management of this disease consists of pharmacological and nonpharmacological modalities. Until recently, pharmacological treatment options have been very limited. However, as mentioned earlier, the development of novel biological therapeutics has revolutionized the management of this disease. In addition, the usefulness of combination therapy with TNF inhibitor and NSAID and DMARD was also reported.<sup>102–104</sup>

Skin and joint manifestations associated with psoriasis and PsA can significantly impact a patient's quality of life. Successful treatment is imperative to improve the signs and symptoms of disease. For patients with moderate to severe active PsA, combination therapy with methotrexate and TNF inhibitors is considered first-line treatment.<sup>105</sup> These new therapeutic concepts for PsA include a high efficacy of combination therapy in those unable to tolerate or who have failed TNF inhibitor treatment.<sup>106</sup>

Relapsing ocular involvement is a major manifestations of BD and occurs in 60–80% of patients, resulting in retinal vasculitis, neuropathy or panuveitis.<sup>107</sup> TNF inhibitors are effective and safe in these patients, especially regarding its corticosteroid- and immunosuppressive drug-sparing effects.<sup>108</sup>

## New Therapeutic Concept

Biological therapeutics are more expensive compared with small molecule drugs, such as JAK inhibitors. Drug costs are more likely to be reduced if generics, such as JAK inhibitors are available.<sup>109–111</sup> Depending on the disease, this approach is likely to become more mainstream. However, autoimmune or self-inflammatory disease have an abnormal cytokine production indicating the potential benefit of biological therapeutics. The recent marketed recycling antibodies are the preparation which was developed so that antibody preparation binds to the antigen repeatedly in vivo.<sup>112</sup> It is thought that even if it leads to such a technique reducing the dosage number of times of biological therapeutics, it becomes useful in economic aspect.

## Conclusions

Cytokines, such as IL-6, have pleiotropic effects and promote various effects in numerous cell types. Cytokines also have overlapping and sometimes redundant effects. Therefore, even if the effects of a specific cytokine are completely blocked, similar effects can be mediated by another cytokine. This might explain why some cases treated with biological therapeutics show no beneficial effect and the blocking a specific cytokine does not always cause serious side effect.

When disease activity is controlled by biological therapeutics, autoimmune diseases can sometimes occur. For example, psoriasis exanthema develops during treatment for RA or BD, a phenomenon termed paradoxical reaction, which is thought to be caused by the overlapping functions of cytokines. When the activity of a disease is inhibited by blocking a specific cytokine, levels of another cytokine are thought to be increased in vivo leading to the induction of autoimmune disease. An example is the onset of MAS by tocilizumab treatment for ASD.

The biological therapeutics contributes to greatly improving convalescence around RA. Other CTD are also experiencing the calming of the disease activity by the development of new biological therapeutics and adaptation expansion of such drugs. In this review, we addressed the current situation of biological therapeutics for CTD-ID including Behcet's disease, psoriatic arthritis, ankylosing spondylitis, anti-neutrophil cytoplasmic antibody-related arthritis, and adult Still's disease, as well as the choice of biological therapeutics in the clinical practice. Further developing biological therapeutics is expected in the scleroderma and the inflammation of muscle-related disease that there remained it.

## Acknowledgments

This review was supported in part by grants (15K08657 and 19K07948 to S.N.) from the Ministry of Education, Culture, Science and Technology of Japan. We thank Edanz (<https://jp.edanz.com/ac>) for editing a draft of this manuscript.

## Disclosure

The authors declare no conflicts of interests regarding the publication of this article.

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