Off-Label Use of Biologics in Rheumatological Disorders

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25.1 Introduction

Biologic drugs are produced from human, animal, or living organisms. Currently, biologics are widely used to treat different diseases. In rheumatic diseases, licensed use of biologic started more than 20 years back for the treatment of Rheumatoid arthritis (RA). European medicines agency (EMA) and the United States food and drug administration (USFDA) are the regulatory agencies for the approval of b-DMARDs in the European Union and the US, respectively. Off-label indication means using a drug to treat a disease or certain manifestation of a disease for which that particular drug is not officially approved. At present, biologics are approved for use in RA, Ankylosing spondylitis (AS), Psoriatic arthritis (PsA), anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis, giant cell arteritis (GCA), etc. Interestingly, biologics are also used as an off-label drug to treat various other rheumatic diseases, and these off-label uses of biologics will be reviewed in this chapter.

25.2 Commonly Used Biological DMARDs in Rheumatic Diseases

Most of the b-DAMRDs target various pro-inflammatory cytokines. b-DMARDs targeting, IL-6 (Tocilizumab), Rituximab (anti-CD 20 monoclonal antibody), Anti-tumor necrosis factor-α (TNF-α) agents, anti-IL-1 agents (Anakinra, Rilonacept, Canakinumab), anti-IL-17A (secukinumab, ixekizumab), or anti-IL-17 receptor (brodalumab) are commonly used for the management of various rheumatic diseases.

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N. Jain, L. Duggal (eds.), *Handbook of Biologics for Rheumatological Disorders*,
https://doi.org/10.1007/978-981-16-7200-2_25

25.2.1 Tocilizumab

- Tocilizumab is a humanized monoclonal antibody, which targets both membrane-bound and soluble IL-6 receptor alpha subunit, thereby preventing the binding of IL-6 with its receptor with subsequent inhibition of downstream signalling of IL-6 [1].
- It is approved for use in RA (moderate to severe) and also in systemic-onset and polyarticular Juvenile Idiopathic Arthritis (JIA).

In 2017 it was approved in both US and EU for the treatment of Giant cell arteritis, the first b-DMARD to get approval for this large vessel vasculitis (LVV). In addition to the approved indications, Tocilizumab has shown promising results in some other rheumatic conditions.

25.2.1.1 Takayasu Arteritis (TA)

- TA is an LVV that classically affects the aorta and its major branches and is associated with significant morbidity. The beneficial role of Tocilizumab, especially in the refractory cases of TA, has been documented in some recent studies [2, 3].
- Apart from symptomatic improvement in TA patients, Tocilizumab therapy can reduce the mean prednisolone dose, ESR value, and Indian Takayasu Arteritis Activity Score (ITAS2010). In some of the patients, there was an improvement of disease status as evaluated by MRI.
- Tocilizumab is more efficacious and has a better safety profile in comparison to the Cyclophosphamide. Few case reports and small case series showed the efficacy and safety of Tocilizumab in pediatric patient with TA as well [4].
- The recently published French TOCITAKA trial concluded that Tocilizumab may be an effective steroid-sparing agent in TA [5]. According to the 2018 EULAR recommendation for the management of LVV, Tocilizumab may be used in relapsing and refractory TA.

25.2.1.2 Adult-Onset Still Disease (AOSD)

- Though any prospective study is still lacking, case reports and series have shown a promising role of Tocilizumab in this disease. Tocilizumab can improve clinical features and reduction in acute phase reactants in AOSD [6].
- Tocilizumab may be more effective for the management of the chronic articular symptoms of AOSD. Importantly, it has been shown that Tocilizumab increases the probability of corticosteroid withdrawal in patients with AOSD [7].
- Tocilizumab is currently used as an off-label drug in steroid-refractory AOSD patients and is a promising drug for the management of conventional treatment-resistant AOSD.

25.2.1.3 Systemic Sclerosis (SSc)

It has been found that serum level of IL 6 correlates with the disease activity and internal organ involvement in SSc.

- In phase 2, randomized, placebo-controlled trial (faSScinate), the efficacy and safety of subcutaneous Tocilizumab were assessed in SSc patients. There was some evidence of less reduction of forced vital capacity (FVC) in the Tocilizumab group; however, reduction in the skin thickening did not show statistical significance.
- In the open-label extension of the same trial, improvement in the skin score and FVC stabilization were maintained. Improvements of both these parameters were also observed among placebo-treated patients who were shifted to the Tocilizumab group in the open-label extension phase [8, 9]. Subsequently, one multicenter, phase 3 trial with subcutaneous tocilizumab 162 mg/week for 48 weeks failed to meet the primary endpoint of improvement of the skin fibrosis; however, it may have some role in preserving the lung function in early SSC [10]. So, it is evident that Tocilizumab may have some role in preventing pulmonary fibrosis in SSC, but not on skin fibrosis. Further studies are required to come to a definite conclusion regarding the utility of Tocilizumab in SSc.

25.2.1.4 Behcet's Disease (BD)

- BD is a multi-organ disease, predominantly affecting skin, mucous membrane, vascular system, eye, and nervous system. Uveitis is commonly seen in BD.
- In a small study, Tocilizumab was used in 11 patients with BD-associated uveitis. There was an improvement in visual acuity, retinal vasculitis, and vitritis in Tocilizumab-treated patients along with a reduction of the number of blood cells in the anterior chamber of the eye. Reduction of steroid dose was also observed [11].

A recent systematic literature review concluded that Tocilizumab could be an alternative treatment option for the refractory ocular, neuro, and vascular symptoms of BD, and also for secondary amyloidosis [12].

25.2.1.5 Polymyalgia Rheumatica (PMR)

- It is a disease of the elderly, characterized by pain and stiffness, especially of shoulder and hip girdles. This condition shows good response to corticosteroid, but adverse effects of steroids is a major concern. Sometimes the disease may be recurring.
- Currently, Tocilizumab is used as a second-line treatment for PMR. A recently published, prospective, open-label study with twenty new-onset PMR patients, Tocilizumab was used as first-line therapy. Results showed good efficacy and steroid-sparing action of Tocilizumab in PMR, indicating a promising role of Tocilizumab in this disease [13]. The large GiACTA trial with 250 patients with GCA received either TCZ weekly or every other week.
- The result showed that TCZ improved clinical outcomes in patients who presented with PMR or cranial symptoms only or both, and another trial showed quick improvement of the inflammatory markers with Tocilizumab in early PMR [14, 15].

25.2.2 Rituximab

Rituximab is a chimeric (murine/human) monoclonal antibody of the IgG1 kappa subclass which is directed against the CD20 antigen expressed on the surface of pre-B cells and mature B cells. After binding with the CD 20, expressed on the cell surface, Rituximab induces apoptosis of these cells and depletion of peripheral B cell pool. It is approved by EMA for the treatment of adult RA patients who are intolerant to or inadequate responders to other DMARDs or anti-TNF therapy. It is also approved for ANCA-associated small-vessel vasculitis. This drug, though not approved, is still frequently used in some of the other rheumatic diseases.

25.2.2.1 Systemic Lupus Erythematosus (SLE)

- SLE is a multisystem autoimmune disease characterized by distinct clinical features and the presence of certain subsets of autoantibodies. The level of anti-ds-DNA antibody, one of the most specific autoantibodies of SLE, positively correlates with the disease activity of SLE.
- In the earlier trials (EXPLORER and LUNAR), Rituximab failed to meet the primary endpoints in SLE. In the EXPLORER trial with 257 SLE patients who had moderate to severe active extra-renal features, Rituximab did not show any difference compared to the placebo, however, a beneficial effect of rituximab was noted among the African American and Hispanic subgroups [16].
- In contrast to the EXPLORER trial, LUNAR was conducted to find the efficacy of Rituximab in class III/IV renal histology SLE patients but failed to achieve the primary outcome. The positive findings of this study were greater reductions in anti-dsDNA and C3/C4 levels and more responders in the Rituximab group [17]. In contrast to these trials, the beneficial role of Rituximab in SLE has been documented by other studies.
- In a retrospective, longitudinal study of lupus patients who were non-responders to standard therapy (LESIMAB), Rituximab therapy achieved response in 62.9% of patients at 6 months. This study highlighted the efficacy of Rituximab in refractory and life-threatening SLE [18].
- The efficacy of Rituximab in patients with active SLE, SLE with active nephritis, SLE with autoimmune cytopenia, biopsy-proven SLE nephropathy, and mild to moderately active SLE has been supported by various studies [19].
- In the study by Condon MB, et al. where 50 consecutive SLE nephritis patients were treated with two doses of rituximab (1 g) and methylprednisolone (500 mg) on days 1 and 15, and Mycophenolate mofetil as maintenance treatment, complete or partial remission was observed in 90% of patients. Among the 45 responders, only two required steroids for more than 2 weeks. In contrast to the EXPLORER and LUNAR trials, this study showed both the efficacy and steroid-sparing effect of Rituximab in SLE nephritis [20].
- It has been found that earlier initiation of Rituximab in SLE patients has good efficacy and steroid-sparing capacity. Long-term follow-up (up to 7 years) study by Gracia-Tello B et al. also supports this notion [21].

- Rituximab is currently not licensed for use in SLE, but it is used as an off-label drug in severe SLE nephritis and autoimmune cytopenia in SLE. Sequential therapy of Rituximab followed by Belimumab (BLyS inhibitor) is theoretically more attractive in the management of SLE.

25.2.2.2 Systemic Sclerosis (SSc)

- The role of the B cells in the pathogenesis of SSc has already been established, so B cell-targeted therapy may be effective in this multisystem disease. Some of the retrospective analyses, case reports, and uncontrolled trials have demonstrated the beneficial effect of Rituximab, especially for skin, lung, and articular involvement [22].
- A recently published open-label, randomized controlled trial from India showed the efficacy and safety of Rituximab as a primary treatment modality for the skin and lung manifestation (ILD) of SSc. In this comparative study between Rituximab and intravenous Cyclophosphamide, improvement in the forced vital capacity (FVC) was observed in the Rituximab group at 6 months, whereas FVC declined in the Cyclophosphamide group. There was a better improvement of the modified Rodnan skin score with Rituximab [23].
- Improvement in the FVC is a very promising finding of this study as lung involvement is one of the important causes of both morbidity and mortality in SSc patients. Further RCTs are required in this aspect, especially regarding the long-term outcome of Rituximab in lung manifestation of SSc before getting its approval.

25.2.2.3 Sjogren Syndrome (SS)

- SS is another autoimmune disease where B cells play an important role in pathogenesis.
- Currently, Rituximab is used for the extra glandular manifestations of SS, including vasculitis, nervous system manifestations, etc.
- An earlier trial showed that Rituximab could reduce fatigue in patients with SS [24]. This finding is, however, not supported by a recent multicenter, randomized, double-blind, placebo-controlled trial in which Rituximab failed to show any benefit in relieving fatigue and pain in SS patients. The unstimulated salivary flow rate was increased in the Rituximab group compared to the placebo, but it was not translated clinically to the improvement of oral dryness [25].
- It is important to note that the efficacy of Rituximab in SS-associated ILD was not assessed in this study, which may be as high as 78% among newly diagnosed SS patients [26].
- One retrospective study documented the efficacy of Rituximab in the improvement of pulmonary function in SS patients. Contrary to the findings of Bowman SJ et al. this study also showed that Rituximab therapy could cause a symptomatic improvement of dryness and fatigue in SS [27].

25.2.2.4 Idiopathic Inflammatory Myositis (IIM)

- IIM is a cluster of multisystem diseases predominantly characterized by the weakness of the proximal muscles. Myositis-specific or myositis-associated autoantibodies are seen in a large number of patients of IIM, suggesting a pathogenic role of B cells in this disease.
- Corticosteroids and second-line immunosuppressants like, Methotrexate, Azathioprine is currently used for the treatment of IIM.
- Considering the role of B cells in the pathogenesis of IIM, Rituximab is used as an off-label drug in this condition. In one RCT, where Rituximab was used in refractory IIM, including both adult and juvenile populations, improvement was seen in 83% of patients [28].
- In addition to the improvement of muscular symptoms, Rituximab may also be effective in the treatment of refractory ILD associated with anti-synthatase syndrome [29].
- Based on these observations, currently off-label use of Rituximab in IIM is restricted to refractory muscle, lung, or skin disease of Dermatomyositis.

25.2.3 Anti-TNF α Agents

TNF-α plays an important role in the pathogenesis of multiple rheumatic diseases, including RA and SpA. It also modulates the production of other cytokines during the process of inflammation, acting as a master regulator of the inflammatory process. Consequently, b-DMARDs targeting TNF-α were started almost three decades back for the treatment of RA, and Etanercept was the first b-DMARD that got approval for the treatment of RA. Anti-TNF-α agents are currently licensed for use in RA, AS, and Psoriatic arthritis. These drugs (except Infliximab) are approved by the EMA for the management of non-radiographic axial SpA, but not by USFDA, until March 2019, when Certolizumab pegol got USFDA approval for this condition. Anti-TNF agents are also used as an off-label drug in certain other rheumatic diseases.

25.2.3.1 Sarcoidosis

A chronic granulomatous disease with multisystem involvement. TNF-α is considered to play a role in the formation of sarcoid granuloma, justifying their off-label use in this disease. Interestingly, not all anti-TNF drugs showed efficacy in Sarcoidosis.

- Golimumab and Etanercept did not show any better efficacy than placebo, whereas Infliximab and Adalimumab were effective. Infliximab has a beneficial role in pulmonary Sarcoidosis, and it can increase FVC in patients with Sarcoidosis; however, improvement can be observed after 6 weeks. Improvement in chest imaging can also be observed after 6 weeks. A better response is seen in patients with elevated C reactive protein and who are on <20 mg of prednisone at the time of initiation of Infliximab [30, 31].

- Adalimumab can also improve FVC in Sarcoidosis, and both of these drugs can improve quality of life and symptom severity in patients. It is also reported that Infliximab may be effective for Sarcoidosis of other locations like ocular, hepatic, nervous system, etc. [32].
- At present, Infliximab is used as an off-label drug in the management of refractory pulmonary Sarcoidosis not responding to steroid and second-line drugs.

25.2.3.2 Uveitis in Rheumatic Diseases

- Uveitis is commonly associated with SpA, JIA (oligoarticular and enthesitis-related arthritis), Behcet's disease, Sarcoidosis. Recurrent uveitis can cause varying degrees of visual impairment, so timely intervention is very much necessary. Studies in animals and humans support the role of TNF-α in the pathogenesis of uveitis.
- Adalimumab is already approved by USFDA for non-infectious uveitis. Infliximab also showed its efficacy in the treatment of uveitis associated with Ankylosing spondylitis and JIA.
- Golimumab showed a favorable result in the management of refractory uveitis associated with SpA.
- The efficacy outcome with Etanercept is somewhat different with a high recurrence rate, and even new-onset uveitis in Etanercept treated patients has been reported [33].
- Infliximab is also useful in refractory posterior uveitis of Behcet's disease, and complete response was noted in 68% of patients in one study. Infliximab can also improve visual acuity in this group of patients [34]. The efficacy and safety of Infliximab for 10 years in refractory uveitis of BD have also been documented [35]. Based on these observations, Infliximab is used as an off-label drug in the management of refractory uveitis associated with certain rheumatic diseases.

25.2.3.3 Behcet's Disease (BD)

- In addition to the management of refractory uveitis, anti-TNF agents also seem to be effective in extraocular features of this variable vessel vasculitis. Few case series and case reports have demonstrated the efficacy of Infliximab in controlling gastrointestinal, central nervous system, and vascular manifestations of BD.
- In Methotrexate and steroid-resistant neuro BD, Infliximab therapy can cause both symptomatic and improvement and regression of parenchymal lesions [36].

25.2.3.4 Kawasaki Disease (KD)

- KD is a childhood-onset, medium vessel vasculitis. The most dreaded complication of KD is coronary artery aneurism (CAA) which can develop in 15–25% of patients without treatment.
- TNF-α again is implicated in the pathogenesis of KD and Infliximab has been used in various studies to find out its efficacy in this disease. Results of these studies are most promising, and one recent trial showed that Infliximab treatment could reduce the incidence of significant CAA, even in IVIG-resistant KD patients. Previously one large RCT showed that the addition of Infliximab as a

primary treatment of KD could reduce fever duration and the Z score of the left anterior descending coronary artery.
- Infliximab can achieve a significantly more defervescence rate than IV polyethylene glycol-treated human immunoglobulin in IVIG-resistant KD [37–39]. Based on these observations, Infliximab is used as an off-label drug in patients with refractory KD.

25.2.4 Anti IL-1 Agents

- Anakinra, an anti-IL 1 b-DMARD was initially approved for the treatment of RA. Based on the important role of IL 1 in the pathogenesis of various autoinflammatory diseases and the success of IL 1 targeted therapy in these diseases, EMA approved this drug for the management of the cryopyrin-associated periodic syndromes (CAPS) and AOSD.
- Canakinumab, another anti-IL 1 agent is approved for the CAPS, systemic-onset JIA, and acute gouty arthritis. The off-label uses of these drugs are much more than its approved indications.
- A retrospective analysis from Italy showed that off-label use of Anakinra and Canakinumab is as high as 86% and 56%, respectively. Anti-IL 1 agents, were used as an off-label drug in patients with BD, Chronic Recurrent Multifocal Osteomyelitis (CRMO), Familial Mediterranean Fever (FMF), and Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) [40].
- One recently published open-label study showed partial efficacy of Anakinra in the treatment of resistant oral and genital ulcers in patients with BD [41]. In a single-center study from Turkey with 36 FMF patients, Anakinra showed its effectiveness in those who were inadequate responders to colchicine, and in FMF-associated amyloidosis [42]. Similarly, in addition to its licensed indications, Canakinumab may be useful in FMF and TRAPS [43, 44]. Anti-IL 1 agents are particularly useful for the primary treatment-resistant autoinflammatory syndromes.

25.2.5 Anti IL-17 Agents

Secukinumab, an IL-17A neutralizing antibody, is already approved for the management of AS, PsA. It is used as an off-label drug in patients with SAPHO syndrome to improve the skin lesion and osteitis seen in this disease [45].

25.3 Conclusion

It is evident from the above discussion is that the b-DMARDs are used as an off-label drug in numerous rheumatic diseases, and the numbers of these off-label uses are not less than their licensed indications. Adequate numbers of RCT s lack in this

context, and the off-label uses of b-DMARDs are mostly based on the positive results of uncontrolled trials or case series. It is expected that the licensed indications of b-DMARDs will expand in the future (Table 25.1).

Table 25.1 Approved and off-label indications of different b-DMARDs

Name of b-DMARD	Approved indications (by EMA or USFDA)	Off-label indications
Tocilizumab	• Adults with moderate to severe active RA not responding to cs-DMARDs or TNF blockers. • Children with active SOJIA and pJIA not responding to conventional therapy. • Refractory GCA	• Refractory TA • AOSD • SSc • BD (for ocular disease) • PMR (second line treatment option)
Rituximab	• Adults with moderate to severe active RA not responding to cs-DMARDs or TNF blockers. (with methotrexate) • In severe, active GPA and MPA (for remission induction and follow-up treatment)	• Refractory SLE nephritis and autoimmune cytopenia in SLE • SSc (for skin and ILD), • Sjogren syndrome (ILD, and probably for fatigue/dryness). • IIM (refractory myositis, skin disease and ILD of ASS)
Anti-TNF agents	• Active RA, • Severe, active AS and PSA (inadequate responders to conventional therapy), • Non-radiographic axial SpA,	• Refractory pulmonary sarcoidosis (IFN and ADA), • Uveitis associated with rheumatic diseases (IFN, ADA, GOL), • BD (resistant ocular, CNS, and GI symptoms), • IvIg refractory KD
Anti IL-1 agents	• RA (not responding to methotrexate), • CAPS • Still's disease	• BD (refractory skin and genital lesions), • FMF • TRAPS • CRMO
Anti IL-17 agents	• AS • PsA • Active Non-Radiographic Axial Spondyloarthritis	• SAPHO syndrome

Abbreviations: *b-DMARD* biological disease-modifying anti-rheumatic drug, *RA* Rheumatoid arthritis, *cs-DMARD* conventional synthetic DMARD, *SOJIA* Systemic-onset juvenile idiopathic arthritis, *pJIA* Polyarticular JIA, *GCA* Granulomatosis with polyangiitis, *TA* Takayasu arteritis, *AOSD* adult onset still disease, *SSc* systemic sclerosis, *BD* Behcet disease, *PMR* polymyalgia rheumatica, *MPA* microscopic polyangiitis, *ILD* interstitial lung disease, *IIM* idiopathic inflammatory myositis, *ASS* anti synthetase syndrome, *AS* ankylosing spondylitis, *PSA* psoriatic arthritis, *SpA* spondyloarthritis, *IFN* Infliximab, *ADA* Adalimumab, *GOL* Golimumab, *KD* Kawasaki disease, *CAPS* cryopyrin-associated periodic syndromes, *FMF* Familial Mediterranean Fever, *TRAPS* Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, *CRMO* Chronic Recurrent Multifocal Osteomyelitis

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