Managing the Patient Being Treated with Biologic Agents for Rheumatic Disease: Pearls for the General Internist

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Rheumatoid arthritis (RA) is a chronic polyarticular disease with systemic consequences leading to impairment and disability. Typical pharmacological treatment consists of nonsteroidal anti-inflammatory drugs and disease-modifying drugs such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. When disease activity persists, the next level of treatment is the biologic drugs. Some of these agents have been available since 1999. Currently, there are nine biologic drugs available for the treatment of RA. Some agents such as the tumour necrosis factor (TNF) inhibitors also have approved indications for psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.

Table 1 shows the nine currently available biologic agents and their indications, pharmacological characteristics, and modes of administration.

The most commonly used agents are the TNF inhibitors. The five agents in this category are all large molecules that require either intravenous or subcutaneous administration. While they all target TNF, they differ in several ways. The products adalimumab, infliximab, golimumab, and certolizumab are antibodies, but they may also bind membrane-bound TNF. Infliximab is the only TNF inhibitor that is administered intravenously. The other TNF inhibitors are either fully human or humanized. Infliximab is a chimeric monoclonal antibody. Immunogenicity with loss of efficacy can be seen when administered without methotrexate in patients with RA. Certolizumab is distinct in that it is a humanized PEGylated Fab fragment targeting TNF. While these agents are very effective, not all patients respond to TNF inhibition.

Currently, other therapeutic targets have been identified including T-cell activation, B-cells, and interleukin-6 (IL-6). Abatacept is a fully human fusion protein that blocks T-cell co-activation by antigen presenting cells. It is administered by

infusion; however, a subcutaneous preparation may be available soon. Rituximab has been used for CD-20-positive lymphoma for many years. It is a chimeric antibody to CD-20-positive B cells. It is administered by two 1,000 mg infusions 15 days apart. Infusions require pre-medication with steroids and antihistamines to minimize infusion-related reactions. Lastly, tocilizumab is a fully human monoclonal antibody targeting the IL-6 receptor and is administered by infusion monthly.

Infliximab

Infliximab is a chimeric antibody with a half-life of 8–9.5 days. In RA, it is administered in a dose of 3 mg/kg intravenously in combination with methotrexate. Loading doses are required at 2 and 6 weeks and then every 8 weeks. For severe disease, doses of 10 mg/kg every 4 weeks may be required, though cost-effectiveness is diminished. For patients with psoriatic arthritis and ankylosing spondylitis, dosing is 5 mg/kg at baseline and 2 and 6 weeks, and then every 8 weeks. In this population, infliximab is effective as monotherapy.^{1–4}

Etanercept

Etanercept is a fully human fusion protein TNF receptor antagonist that binds soluble TNF and lymphotoxin- α . It is administered subcutaneously at 50 mg once or 25 mg twice weekly. The half-life is 4 days. Etanercept can be used as monotherapy but is typically used in combination with methotrexate. The Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study found superior efficacy for etanercept when combined with methotrexate.⁵

In order to control psoriasis, a dose of 50 mg twice weekly is used for the initial 12 weeks. Etanercept is similarly effective in psoriatic arthritis and ankylosing spondylitis.^{6,7}

Table 1. Biologics' Product Characteristics

	Adalimumab	Etanercept	Infliximab	Certolizumab	Golimumab	Abatacept
Trade name	HUMIRA	Enbrel	Remicade	Cimzia	Simponi	Orencia
Company	AbbVie	Amgen	Centocor Inc. Janssen	UCB	Janssen	Bristol-Myers Squibb
Molecule type	Fully human monoclonal antibody	Fully human fusion protein	Chimeric monoclonal antibody	Humanized PEGylated Fab fragment	Fully human monoclonal antibody	Fully human fusion protein
Target	TNF- α	TNF- α	TNF- α	TNF- α	TNF- α	T cell
Dosing	40 mg EOW	50 mg/mL q1w or 25 mg/mL q2w	3–7.5 mg/kg q8w	200 mg q2w or 400 mg q4w EOW most probable	50 mg monthly	125 mg/mL weekly following a single IV loading dose
Delivery method	Self-injection SC (PFS and pen)	Self-injection SC (PFS and pen)	120-minute infusion	Self-injection SC	Self-injection SC (pen)	30-minute infusion, self-injection SC
Indication	RA, JIA, AS, PsA, Ps, Crohn's	RA, JIA, AS, PsA	RA, AS, Crohn's, UC, PsA, Ps	RA	RA, AS, PsA	RA, JIA

AS = ankylosing spondylitis; EOW = every other week; IL = interleukin; JIA = juvenile idiopathic arthritis; PFS = prefilled syringe; Ps = psoriasis;

PsA = psoriatic arthritis; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

Source: Data mostly from the Canadian Pharmacists Association; *Compendium of Pharmaceuticals and Specialties*; Ottawa (ON): The Association; 2011.

Adalimumab

Adalimumab is a human monoclonal antibody that binds both soluble and membrane-bound TNF. The half-life is 12 days. The typical dose is 40 mg subcutaneously every other week. While effective as monotherapy, its efficacy is enhanced in combination with methotrexate in RA and PsA.⁸ Adalimumab is also effective as monotherapy in psoriatic arthritis and ankylosing spondylitis.^{9,10}

Golimumab

Golimumab is a human monoclonal antibody with specificity for TNF. Its half-life is 14 days, but it is administered every 4 weeks as a 50 mg dose subcutaneously.

This agent has been shown to be effective in the treatment of RA, psoriatic arthritis, and ankylosing spondylitis.^{11–13}

Certolizumab Pegol

Certolizumab pegol is a humanized PEGylated Fab fragment anti-TNF monoclonal antibody. The Fab antibody portion is fused to polyethylene glycol (PEG) molecule. This PEGylation process delays the clearance of the molecule, resulting in a half-life of 14 days. Standard dosing is 400 mg at weeks 0, 2, and 4, and then 200 mg weekly administered subcutaneously.

Efficacy has been shown in RA with or without methotrexate.^{14,15}

Tocilizumab

Tocilizumab is a humanized antihuman antibody targeting the IL-6 receptor (IL-6R). The drug is administered intravenously at 4 mg/kg or 8 mg/kg monthly.^{16,17} A large research program has shown tocilizumab to be effective in treating signs and symptoms of RA as well as retarding radiographic progression. Tocilizumab

has also been shown to be effective as monotherapy and, in one trial, was found to be superior to methotrexate.^{17,18}

Infections occur at similar rates to other biologic disease-modifying anti-rheumatic drugs (DMARDs). The most common infections reported have been cellulitis, pneumonia, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis.¹⁹ Abnormal liver function ($>3 \times$ normal levels) has been noted when tocilizumab is used in combination with DMARDs (5–6%) but less often with monotherapy (1%).²⁰ Neutrophil count below 1,000/mm³ occurred in up to 3.4% with tocilizumab plus DMARD compared with 0.1% in placebo plus DMARD in 24-week controlled trials. There did appear to be a relationship between neutropenia and serious infections.¹⁹ No increased incidence of malignancy, tuberculosis reactivation, or hepatitis was seen. Rare events including gastrointestinal perforation related to diverticular disease were noted, but confounders were the use of steroids, non-steroidal anti-inflammatory drugs, and methotrexate.

Rituximab

Rituximab has proven to be a novel therapy in treating RA. Rituximab is a chimeric monoclonal antibody targeting a B-cell surface marker CD20. With a single rituximab infusion, B cells are rapidly depleted from the peripheral blood and, subsequently, synovial tissues in most but not all patients.²¹

The treatment regimen is a course of 1,000 mg given on days 1 and 15, together with methotrexate. Clinical response is most robust in rheumatoid factor–positive patients. The mean duration of response or retreatment interval is 6–12 months.^{22–24}

While B-cell depletion therapy has been associated with some reduction in immunoglobulin levels, this has not been

Rituximab	Tocilizumab	Anakinra
Rituxan	Actemra	Kineret
Roche	Roche	Sobi
Biogen Idec	Chugai	
Chimeric monoclonal antibody	Humanized monoclonal antibody	Monoclonal antibody (IL-1 receptor antagonist)
B cell	IL-6R	IL-1 receptor
1,000 mg IV q2w Subsequent infusions repeated as necessary	4 or 8 mg/kg monthly	100 mg daily
195- to 255-minute infusion	60-minute infusion	Self-injection SC
RA	RA	Rarely used in RA now; check package insert

associated with an increased infection risk in this population. Nonetheless, current recommendations are that all recommended vaccines should be given prior to treatment to improve efficacy. Vaccination administered in close proximity to rituximab use is less effective.^{25,26} The overall rate of serious infection reported in a longitudinal safety study was 4.31 infections/100 patient-years, consistent with rates seen with other biologic DMARDs. Viral reactivation, a concern with B-cell depletion, was not increased in this population. Progressive multifocal leukoencephalopathy (PML), a rare disease caused by reactivation by the JC virus, was reported in one patient who also received cancer chemotherapy.²⁷

Overall there was no excess mortality, cardiovascular events, tuberculosis (TB), or evidence of malignancy reported. Repeated courses of treatment did not result in any increase in serious adverse events.²⁷

Abatacept

Abatacept is a fully human fusion protein (cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin G1 [CTLA4Ig]) whose mode of action is to block T-cell activation. This is accomplished by binding to CD80 and CD86 on antigen presenting cells, thus blocking their binding with CD28 on T cells and their subsequent activation.

Abatacept is administered intravenously in a dose of 10 mg/kg over 30 minutes. Infusion reactions are uncommon and infusion can be undertaken in the home or infusion centre.²⁸

Summary

A recent meta-analysis showed that there is significant efficacy for the approved biologic drugs compared with placebo, based

Table 2. Meta-analysis of Efficacy with Biologics in RA: ACR50

Biologic	No. of Studies	OR (95% CI)	Heterogeneity
Abatacept	6	2.98 (1.79–4.97)	$I^2 = 0\%$
Adalimumab	8	3.70 (2.40–5.70)	$I^2 = 77\%$
Anakinra	3	1.68 (0.83–3.41)	$I^2 = 84\%$
Etanercept	4	4.97 (2.70–9.13)	$I^2 = 75\%$
Infliximab	3	2.92 (1.37–6.24)	$I^2 = 16\%$
Rituximab	3	4.10 (2.02–8.33)	$I^2 = 17\%$
Overall	27	3.35 (2.62–4.29)	$I^2 = 69\%$

ACR50 = 50% improvement in the American College of Rheumatology symptomatic criteria; CI = confidence interval; OR = odds ratio.

Source: Adapted from Singh et al.²⁹

Table 3. Meta-Analysis of Efficacy with Biologics in RA: Safety*

Biologic	No. of Studies	OR (95% CI)	Heterogeneity
Abatacept	6	1.24 (0.88–1.76)	$I^2 = 15\%$
Adalimumab	8	1.54 (1.12–2.12)	$I^2 = 0\%$
Anakinra	5	1.67 (1.22–2.29)	$I^2 = 0\%$
Etanercept	4	0.82 (0.56–1.19)	$I^2 = 94\%$
Infliximab	3	2.21 (1.28–3.82)	$I^2 = 55\%$
Rituximab	3	1.34 (0.65–2.76)	$I^2 = 0\%$
Overall	29	1.39 (1.13–1.71)	$I^2 = 15\%$

CI = confidence interval; OR = odds ratio.

*Placebo is safer.

Source: Adapted from Singh et al.²⁹

on demonstrating at least a 50% improvement in patient and physician reported criteria of the American College of Rheumatology (ACR 50). The study also showed that placebo is safer for all agents except etanercept (odds ratio 0.82) based on withdrawals for adverse events.²⁹

These agents have all been shown to retard radiographic progression, a hallmark of future disability in RA.³⁰ Table 2 presents the efficacy of biologics in RA related to a 50% improvement in the American College of Rheumatology symptomatic criteria (ACR50). Table 3 presents the efficacy of biologics related to safety.

Clinical Considerations

Infections in Patients Using Biologic Drugs

Overall, the risk of infections is greater in patients taking biologic drugs.²⁹ Abatacept seems to be less of a concern; however, the product monograph warns about increased pulmonary complications, including infections in those with chronic obstructive lung disease (COPD). The risk for infection seems to be greatest in those beginning treatment, and it decreases after the first year.^{31,32}

When a patient using a biologic agent presents with infection, discontinuing the agent is prudent. One must recognize that the half-life of these agents varies from 4 days for etanercept to 12–14 days for adalimumab, golimumab, and certolizumab. Most infections respond to treatment before complete clearance of the drug is achieved.

The types of infections seen in patients on biologic therapy mirror those seen in the general population. Opportunistic infections with *Mycobacterium tuberculosis* are of concern, as disseminated disease or reactivation of latent disease is seen in all clinical trials with the TNF antagonists. It is important to consider other risk factors for TB such as country of origin or travel to countries where TB is endemic, or specific at-risk populations (e.g., Aboriginal). Screening is recommended for all patients prior to the use of the anti-TNF therapies abatacept and tocilizumab.³³ While other opportunistic infections have been reported with biologic agents, disease severity, the use of corticosteroids, and co-morbidities contribute to this risk.³⁴

Perioperative Care

When elective surgery is being considered in patients on immunosuppressive therapy, infection risk may be increased. Concomitant medications such as methotrexate and corticosteroids may increase the risk for infection and impair wound healing. The merits of discontinuing treatment must be balanced against the risk of disease flares.

The Canadian Rheumatology Association guidelines recommend that biologic drugs be held prior to surgical procedures. The timeline must take into consideration the individual patient, the nature of the surgery, and the drug's half-life. The biologic can be resumed in the absence of infection and if wound healing is satisfactory.³³

The American College of Rheumatology recommends that biologics should not be used 1 week prior to and 1 week after surgery, taking into consideration the pharmacokinetics of the agent and the infectious risk of the surgery.³⁵

The British Society of Rheumatology recommends the following: "Treatment with infliximab, etanercept and adalimumab should be withheld for 2 to 4 weeks prior to major surgical procedures. Treatment may be restarted post-operatively if there is no evidence of infection and once wound healing is satisfactory."³⁶

Cardiovascular Risk

A number of publications have highlighted the increased cardiovascular risk inherent in patients with RA. The estimated risk is 1.5- to 2-fold and is similar to that in patients with diabetes mellitus.³⁷

Recently, the use of TNF inhibitors has been shown to reduce the incidence of cardiovascular events. The true benefit was most evident in treatment responders, suggesting that control of inflammation is responsible for the risk reduction.^{37,38}

Those individuals at risk of heart failure or who have New York Heart Association class III or IV heart failure should not receive TNF inhibitors. TNF is increased in CHF, and studies using infliximab for CHF showed increases in exacerbation of CHF and in death.^{39,40}

Malignancy Risk

The issue of malignancy risk has been closely scrutinized in clinical trials, registries, and meta-analyses. Patients with RA are at a higher risk for lung cancer and lymphoma.⁴¹ The risk of lymphoma correlates with disease activity. With respect to biologic agents, all but one meta-analysis showed no increase in malignancies, including lymphomas. Rare cases of hepatosplenic lymphoma have been reported in patients with inflammatory bowel disease, in association with infliximab and adalimumab use. Observational studies have reported increased frequencies of non-melanoma skin cancers.^{42–45}

Viral Complications

Several databases in Spain, Germany, and Canada have reported higher risks of varicella infection in patients with RA.^{46–48} TNF inhibitors and rituximab are associated with an increased risk of hepatitis B reactivation. There are rare reports of PML in patients using rituximab. Of 57 reported cases, most were related to the use of rituximab for chemotherapy. There were two cases in patients with systemic lupus erythematosus (SLE) and one case involving a patient with RA. There is no screening or treatment available for this rare but fatal condition.⁴⁹

Vaccination

The risks of infections and associated mortality can be mitigated by the prior use of vaccination in patients prescribed biologic agents to maximize their effectiveness. In the case of rituximab, if immunization is not achieved pre-treatment, then a delay in immunization offers better protection.^{50,51}

The Canadian Rheumatology Association guidelines recommend annual influenza vaccination and pre-treatment vaccination against pneumococcal disease with inactivated/killed vaccines. For high-risk populations, hepatitis B vaccination is recommended. Currently, the herpes zoster vaccine is a live vaccine and is to be avoided in patients who are using biologic agents.³³ An inactivated vaccine is in development, so this recommendation may change.

Conclusion

The following is a summary of key points related to the use of biologics:

- Biologic agents are effective in patients with rheumatic disease such as RA, psoriatic arthritis, and ankylosing spondylitis.
- Infection risk is greater for patients on biologic agents than on DMARDs alone, though co-morbid conditions and the use of corticosteroids play a role. Biologic agents should be held in the face of active infection.
- Screening for latent TB is recommended in all patients prior to treatment.
- TNF inhibitors and other biologic drugs should be held when surgery is considered; the duration depends on the half-life of the agents and time for wound healing.
- The risk of lymphoma in general is not increased with the use of TNF inhibitors, although rare cases of hepatosplenic lymphoma have been reported in patients with Crohn's disease.
- Vaccinations should be given prior to treatment with biologic agents. Live vaccines are to be avoided in patients on treatment.

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