Chapter 21

MONOCLONAL ANTIBODIES IN RHEUMATOLOGY

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ABSTRACT

The pathogenesis of autoimmune rheumatic diseases (ARDs) involves the interaction and activation of immune cells with the release of multiple inflammatory cytokines such as tumour necrosis factor α (TNF -α) and interleukins. The advances in molecular biology enabled the development of pivotal molecules called monoclonal antibodies (mAbs), which target various mechanisms of disease pathogenesis. The advent of mAbs has revolutionised the management of ARDs, as these therapeutic agents have shown benefits in controlling the symptoms of some patients who lost response or had side-effects to conventional disease modifying anti-rheumatic drugs (cDMARDs).

This chapter reviews the use of mAbs in ARDs. We will focus on the type, mode of action, clinical efficacy and safety profile of mAbs, with particular emphasis on TNFα, interleukin 6 (IL6) interleukin 17/23 (IL17/23) axis
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and T cell co-stimulatory blockade, as well as and B cell depletion therapies. Additionally, we will discuss the emerging biosimilars which can potentially have a positive impact on the socioeconomic burden of ARDs.

Keywords: *autoimmune rheumatic diseases, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, monoclonal antibodies, adalimumab, etanercept, infliximab, golimumab, certolizumab, anakinra, tocilizumab, sarilumab, ustekinumab, secukinumab, ixekizumab, abatacept, rituximab, biosimilars*

INTRODUCTION

Autoimmune diseases are heterogeneous disorders characterized by abnormal immune response causing damage or dysfunction to target organs. Rheumatoid arthritis (RA) if the prototypical autoimmune rheumatic disease (ARD) systemic lupus erythematosus (SLE), inflammatory myopathies, systemic sclerosis or vasculitis are examples of ARDs with various organ and system involvement. ARDs are associated with significant morbidity and mortality in patients, and most often affect women (1).

The aim of treatment in ARDs is remission or low disease activity if remission cannot be achieved. The ultimate aim is minimal joint damage accrual, reduced pain and maintenance of function (2). The first-line treatment for ARDs is focused on the use of conventional disease modifying anti- rheumatic drugs (cDMARDs), such as methotrexate, sulfasalazine and hydroxychloroquine. These use of these treatments has been based on clinical evidence for efficacy in various rheumatic conditions rather than being developed based on the pathophysiology of ARDs. For example, methotrexate was originally used as a cancer drug, but found to effective in lower doses in rheumatic diseases. cDMARDs are used as monotherapy or in combination using a step- up treatment strategy.

Although a lot of patients respond adequately to these cDMARDs, a significant proportion of patients still have active disease, requiring additional therapy. The advances in the understanding of ARD pathogenesis led to the discovery of key target molecules with fundamental roles in initiating, propagating, and maintaining the autoimmune process, such as the tumour necrosis factor alpha (TNFα) and interleukin 6 (IL6). Monoclonal antibodies (mAbs) are genetically engineered biologic molecules targeting pro-inflammatory pathways relevant to ARDs which can be used as monotherapy or in combination with DMARDs (3).

TYPE OF MONOCLONAL ANTIBODIES USED IN RHEUMATOLOGY

Immunoglobulins (antibodies) are multifunctional proteins of the immune system produced by B lymphocytes. They comprise two heavy and two light chains with variable domains that bind antigens, and Fc constant domains

that binds to the Fc receptors of various effector cells. There are five immunoglobulin isotypes determined by the constant region of the heavy chains: IgM, IgG, IgA, IgD, and IgE.
Most antibodies produced as part of the normal immune response are polyclonal, meaning that they are produced by a number of different B cells, and as a result, they have different binding affinity for the target antigen. Biotechnology advances have enabled the production of large quantities of an antibody from a single B-cell clone called mAb. mAbs can bind to specific antigens, either soluble or cell-surface targets, enabling selective inhibition of targeted pathogenic mechanisms (4).
The first generation of therapeutic mAbs were murine derived. However, their effectiveness in patients was limited due to increased immunogenicity risk. This means that the murine components of mAb could act as haptens leading to an antibody response (5).

The continuous advancement in recombinant DNA technologies has led to the reduction of the immunogenicity of mAbs in humans, by developing two different types of mAbs, chimeric (fused human-mice mAbs) and humanised. The chimeric antibodies were developed by replacing the constant region of murine mAbs with human components and the humanised mAbs constitute entirely of human sequences, except for the antigen binding region. Subsequently, the advanced antibody engineering achieved the production of fully human antibodies. Adalimumab is the first fully human antibody approved in 2004 for the treatment of RA (6). Currently, most mAbs on the market are humanised or fully human (Figure 1). In order to improve the half-life, some mAb have been pegylated (e.g. Certolizumab is a Fab fragment of mAb anti-TNFα lacking the Fc portion and linked to polyethylene glycol) (7).

Figure 1: Monoclonal Antibody Structure

MODE OF ACTION OF MONOCLONAL ANTIBODIES

I) Tumour Necrosis Factor Alpha (TNFα) Inhibitors

TNFα is a cytokine produced chiefly by activated macrophages, although it can be produced by numerous immune, non-immune and tumour cells. TNFα must bind two receptors, TNFR1 (TNF receptor type 1) and TNFR2 to exert its biological function. Both receptors are transmembrane glycoproteins with similar extracellular domains, and distinct intracellular domains. TNFα is a potent inducer of the inflammatory response activating the synthesis and recruitment of a large range of pro inflammatory cytokines, such as interleukin 1 (IL1) and several chemotactic cytokines (chemokines). The most convincing evidence to date that TNFα is central in the pathogenesis of arthritis is the effective use anti-TNF agents in the treatment of RA for many years (8).

Adalimumab (Humira™, Abbvie, 2002) and **Golimumab** (Simponi™, Janssen, 2009) are both human-sequence IgG antibodies. They bind to soluble and transmembrane forms of TNFα and interfere with the inflammatory cascade.

Etanercept (Enbrel™, Amgen, 1998) is a human TNF-receptor fusion protein. It consists of two extracellular domains of human soluble TNF receptor 2, which binds to TNF and an Fc fragment of human IgG. It neutralises the TNF biological function by binding to both TNF α and β.

Infliximab (Remicade™, Janssen, 1998) is a chimeric mAb, 25% murine and 75% human derived with a constant human region (IgG1) and a variable mouse region with affinity for both soluble and transmembrane TNFα.

Certolizumab pegol (Cimzia™; UCB, 2008) contains a TNF-specific Fab fragment of a humanised mAb, which binds to both soluble and membrane-bound TNFα and a fragment conjugated to polyethylene glycol to enhance its plasma half-life.

II) Interleukin/interleukin receptor blockers

Interleukin 1 (IL1) inhibition

Anakinra (Kineret™, Sobi, 2001) is an engineered human interleukin 1 receptor (IL1R) antagonist protein. IL1 is a pro-inflammatory cytokine. Based on studies in animal models, it was hypothesized that IL1 plays a fundamental role in RA-associated cartilage and bone destruction and subsequently, IL1R inhibition resulted in a modest inhibition of joint swelling and inhibition of radiographic progression of bone lesions in RA (9)**.** Although, Anakinra was initially used for RA treatment (10), the 2009 NICE (National Institute for Health and Care Excellence) guideline appraised the level of evidence and concluded that Anakinra is not cost-effective or recommended for RA treatment. (11). Anakinra is used to treat other ARDs, such as Adult- Onset Still's disease, periodic fevers and auto inflammatory diseases (Familial Mediterranean Fever, Hyperimmunoglobulin D syndrome, Schnitzler's syndrome and TNF receptor-associated periodic syndrome) (12)

Interleukin 6 (IL6) Inhibition

IL6 acts a pro-inflammatory cytokine in autoimmune rheumatic diseases and binds to both membrane-bound (IL6R) and soluble receptors (sIL6R). IL6 is directly involved in the development of synovitis and is the most abundantly present cytokine in the rheumatoid joint. IL6 is also an important mediator of systemic features, such as fever, by stimulating the production of acute-phase protein by hepatocytes (13).

Tocilizumab (RoActemra™, Roche, 2010) and **Sarilumab (**Kevzara™, Sanofi, 2017) are both humanised mAbs against the interleukin-6 receptor (IL-6R).

Interleukin 12/23 inhibition (IL12/23)

The IL12/23 common pathway has been found to play a determinant role in the induction of inflammation in seronegative spondyloarthritis. In particular, interleukin 23 (IL23) promotes the differentiation of naïve T helper cells into Th17 cells and the production of several inflammatory cytokines such as IL17 and IL22, whereas IL12 induces the development of Th1 cells with the concomitant secretion of cytokines such as interferon-γ (14).
Ustekinumab (Stelara™, Janssen, 2016) is a human mAb that acts as a cytokine inhibitor by targeting the IL12 and IL23. Ustekinumab binds to both IL12 and IL23 interfering in the interaction with their receptors and thereby blocking the Th1 and Th17 inflammatory pathways.

Interleukin 17 (IL17) inhibition

The IL17 is a cytokine family with six members (from IL17A-F). Increased IL17A levels have been reported in serum and synovial fluid of RA patients and animal models for inflammatory arthritis demonstrated that blocking endogenous IL17A prevents or decreases arthritis (15). Various mAbs that directly target IL17A, its receptor or inhibit both IL17A and IL17F are currently available.
Secukinumab (Cosentyx™, Novartis, 2015) is a fully human mAb that selectively neutralises IL17A.
Ixekizumab (Talz, ™, Eli Lilly, 2016) is a humanized IgG4 mAb that binds IL17A and blocks the interaction with its receptor IL17RA, and consequently the biological activity of IL17A.
Bimekizumab (UCB-4940, UCB) is a fully human mAb that selectively neutralises IL17A and IL17F currently trialled in psoriatic arthritis and ankylosing spondylitis

III) Co- Stimulatory Signal Inhibition

Abatacept (Orencia™, Bristol-Myers Squibb, 2005) is a fusion protein composed of the Fc region of the immunoglobulin IgG fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). In order for a T cell to be activated and produce an immune response, an antigen presenting cell must present the CD80 or CD86 molecule to the T cell in addition to the antigen (co- stimulation of T cell). Abatacept binds to the CD80 and CD86 molecule, thus preventing the T cell activation (16).

IV) B- Cell Depletion Therapy

Rituximab (Rituxan™, Genentech and Biogen – USA, Canada & Japan, 1997; Mabthera™, Roche – Europe, 1998) is a mouse-human chimeric anti-CD20 mAb. CD20 is a cell surface protein that is highly expressed by naive, mature, and memory B cells, but not by hematopoietic stem cells, early B cell precursors and plasma cells. Therefore, only CD20+ B cells may be depleted by rituximab without preventing their regeneration whilst

potentially eliminating the autoantibody-producing clones. Peripheral B cells start repopulating in 6 to 9 months after treatment in RA patients (17). Rituximab is used for patients with refractory renal and non-renal lupus based on expert consensus (18, 19) despite the negative results of two large trials, LUNAR (clinical trial of patients with lupus nephritis) (20) and EXPLORER (clinical trial which included of non-renal patients) (21).

V) B-lymphocyte stimulator (BLyS) inhibition

Belimumab (Benlysta™, GSK, 2011) is a human mAb that decreases the number of B cells by inhibiting the B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS). BLys or BAFF is secreted by a variety of cells and interacts with three membrane receptors on B lymphocytes, BAFF- receptor, BCMA (B cell maturation antigen) and TACI (transmembrane activator and calcium modulator and cyclophylin ligand interactor). This interaction promotes the survival, proliferation and differentiation of B cells (22).

New therapeutic targets

There are several new biologic agents that are currently tested in clinical trials for various indications: e.g. anti BAFF-R mAb for RA and Sjogren's syndrome, anti CD40 mAb blockade for lupus nephritis and Sjogren's syndrome, fully human anti CD20 mAbs for use in RA and SLE, as well as new IL6 blockage agents for use in RA and vasculitis.

It is worth mentioning the small molecules inhibitors, such as the Janus Kinase Inhibitors, which were recently introduced in rheumatology as new targeted therapeutic options. These treatments have been developed to target pro-inflammatory intracellular pathways leading to various pathological processes in ARDs. They are different from mAbs in terms of chemical structure, mode of action, distribution and mode of administration. Small molecules are able to enter cells easily because of their low molecular weight and subsequently block the downstream activation of various pathways. The most established small molecules are the Janus kinase (JAK) inhibitors, which target one or more of the JAK family enzymes (JAK1, JAK2, JAK3, TYK2) and thereby interfere with multiple cytokines which utilize the JAK enzymes for signalling. These molecules have a similar safety profile with the TNF inhibitors, including increased risk of infections and viral and latent tuberculosis reactivation (23).

Table 1. Marketing authorization of Monoclonal Antibodies in the NHS

Monoclonal Antibody, FDA registration year	Clinical indications	Route of administration	Doses	Pregnancy (24)	Breastfeeding (24)
TNFα Inhibitors					
Adalimumab, 2002 **(25-28)**	Severe RA when inadequate response to, or intolerance to previous therapy with cDMARDs or biologics Active and progressive PsA when the patient has peripheral arthritis with three or more tender joints and three or more swollen joints and the psoriatic arthritis has not responded to adequate trials of at least two cDMARDs, administered either individually or in combination. AS when inadequate response to or intolerance of NSAIDs	SC injection	40 mg every other week	Until the end of the second trimester. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age	Women should not be discouraged from breastfeeding on TNFα inhibitors
Etanercept, 1998 **(25-28)**		SC injection	25 mg twice weekly or 50mg weekly		
Infliximab, 1998 **(25-28)**		IV infusion	3 mg/kg, with initial doses at 0, 2 and 6 weeks and then every 8 weeks thereafter. Alternatively, 3 mg/kg every 4 weeks.		
Golimumab, 2009 **(25, 27-29)**		SC injection	50 mg once a month	Unlikely to be harmful in the first trimester	
Certolizumab, 2008 **pegol (25, 28, 30, 31)**		SC injection	400 mg at 0, 2 and 4 weeks, followed by maintenance doses of 200 mg every 2 weeks.	Compatible with all three trimesters of pregnancy	
IL1 Inhibition					
Anakinra, 2001	Periodic fevers and auto inflammatory diseases when standard treatment has failed or in whom standard treatments are poorly tolerated (12)	SC injection	100mg daily	Unintentional exposure in the first trimester is unlikely to be harmful	There are no data on Anakinra use in breastfeeding
	Adult- Onset Still's disease in patients with inadequate response to or intolerance of previous standard immunosuppressive	SC injection			

	therapy (glucocorticoids and cDMARDs) or where standard therapies are contraindicated (32)				
IL6 Inhibition					
Tocilizumab, 2010	Severe RA with inadequate response to, or intolerance to previous therapy with cDMARDs or biologics (33)	IV infusion	8 mg/kg every 4 weeks.	Tocilizumab should be stopped at least 3 months before conception, but exposure early in the first trimester is unlikely to be harmful	There are no data on Tocilizumab use in breastfeeding
	Adult- Onset Still's disease in patients with inadequate response to or intolerance or contradiction of previous standard immunosuppressive therapy (glucocorticoids and cDMARDs) (32)	IV infusion	Between 4mg/kg every four weeks to 8mg/kg every two weeks. Stable patients could be considered for SC tocilizumab.		
	Giant Cell Arteritis for patients with relapsing or refractory disease (used with a tapering course of glucocorticoids or as monotherapy (34)	SC injection	162 mg SC injection once weekly.		
Sarilumab, 2017	Severe RA with inadequate response to, or intolerance to previous therapy with cDMARDs or biologics (35)	SC injection	200 mg once every 2 weeks	No BSR guidelines available	
Interleukin 12/23 inhibition					
Ustekinumab, 2016	Active PsA when inadequate response to one or more TNFα inhibitors or TNFα inhibitors are contraindicated, but would otherwise be considered as per TNFα inhibitors clinical indications (36)	SC injection	45 mg at week 0, followed by a dose 4 weeks later and further doses every 12 weeks thereafter	No BSR guidelines available	
IL17 Inhibition					
Secukinumab, 2015	Active PsA when inadequate response to one or more TNFα inhibitors or TNFα inhibitors are contraindicated, but would otherwise be considered as per TNFα inhibitors clinical indications (31) AS in adults with inadequate response to NSAIDs or TNFα inhibitors (37)	SC injection	150 mg with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing	No BSR guidelines available	

Ixekizumab, 2016	Active PsA when inadequate response to one or more TNFα inhibitors or TNFα inhibitors are contraindicated, but would otherwise be considered as per TNFα inhibitors clinical indications (38)	SC injection	160 mg (two 80 mg injections) at week 0, followed by 80 mg daily every 4 weeks thereafter.	No BSR guidelines available	
Co- Stimulatory Signal Inhibition					
Abatacept, 2005	Severe RA when inadequate response to, or intolerance to previous therapy with DMARDs or biologics (25, 26)	SC injection	125 mg SC injection once weekly	Unintentional exposure early in the first trimester is unlikely to be harmful	There are no data on ABA use in breastfeeding
B- Cell Depletion Therapy					
Rituximab, 1997	Severe RA (26) when inadequate response to, or intolerance of, other DMARDs, including at least one TNFα inhibitor Refractory SLE, vasculitis, Sjogren's syndrome	IV infusion	Course of Rituximab: (two 1000 mg IV infusions given 2 weeks apart) at intervals of no less than 16 weeks	Rituximab should be stopped 6 months before conception	There are no data on Rituximab use in breastfeeding
B-lymphocyte stimulator (BLyS) Inhibition					
Belimumab, 2011	Active autoantibody-positive SLE with muco-cutaneous and musculoskeletal involvement (39)	IV infusion	10 mg/kg on days 0, 14 and 28, and at 4-week intervals thereafter	Unintentional exposure early in the first trimester is unlikely to be harmful	There are no data on Belimumab use in breastfeeding
TNF= Tumour Necrosis Factor, RA= Rheumatoid arthritis, PsA= Psoriatic Arthritis, cDMARDS= conventional Disease Modifying Anti-Rheumatic Drugs, NSAIDs= Non-Steroidal Anti-Inflammatory Drugs, IL= Interleukin, SLE= Systemic Lupus Erythematosus					

BIOSIMILARS

Although the use of mAbs has revolutionized the treatment of ARDs (7), the high cost of these treatments limits their widespread use due to healthcare budget restrictions in many countries (40). Furthermore, biological medicines are currently associated with the largest cost and cost growth in the whole NHS (National Health System) medicines budget in the UK. The introduction of less costly biosimilars due to the patent expiration on many biologic therapies is likely to improve patient access to biologic therapy (41).

The NHS England defines a biosimilar as a biological medicine which has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of that originator (42).

The EMA (European Medicines Agencies) is responsible for evaluating the majority of applications for marketing authorization of biosimilars in the European Union (EU). A biosimilar is required to demonstrate through comprehensive comparability studies with the reference biological medicine that it is highly similar to the reference medicine in terms of structure, physicochemical characteristics, biological activity and has equivalent efficacy with a similar safety profile (43).

The Infliximab (Remicade) biosimilar CT-P13 (Remsima and Inflectra) was the first TNFα inhibitor biosimilar which reached the European market in 2013 followed by a second Infliximab biosimilar, SB2 (Flixabi), in 2016. The Etanercept (Enbrel) biosimilar SB4 (Benepali) and most recently four Adalimumab biosimilars Amgevita, Hyrimoz, Hulio and Imraldi have also received marketing authorization in the EU (44).

NHS Improvement strategy is supporting the increased uptake of biosimilar medicines, as the use of biosimilars in the NHS can save up to £300m each year, enabling more patients to have access to licensed treatments. The recommendation is that the responsible prescriber in liaison with the individual patient decides whether a reference or biosimilar biologic will be prescribed in accordance with the approved indications on the summary of product characteristic (42).

Additionally, the increased biosimilar use in the last few years has raised new issues, such as the nocebo effect, encountered when switching a patient from an originator to a biosimilar product. Nocebo effect is defined as the incitement or the worsening of symptoms induced by any negative attitude from non-pharmacological therapeutic intervention or active therapies (45). Multiple approaches have been adopted by different hospitals in order to minimise the impact of nocebo effect, such as group information meetings about the switch and individual counselling during their routine clinical appointment (46).

In conclusion, it must be recognised that the recently introduced biosimilars are not identical, but highly similar to the reference medicine, therefore, vigilance and good quality long-term clinical data are required to provide adequate information regarding their efficacy and safety profile in real-life.

SAFETY AND TOXICITY PROFILE OF MONOCLONAL ANTIBODIES IN RHEUMATOLOGY

Table 2. Safety of Monoclonal Antibodies in Rheumatology

Safety profile	Safety precautions	Monoclonal antibody
Hypersensitivity reactions	NA	All mAbs, especially Rituximab and Infliximab
Injection site reactions	NA	All mAbs
Immunosuppression	Live vaccines should not be given concurrently	All mAbs
Increased risk of infection	MAbs should be discontinued in the presence of serious infections but can be recommenced once the infection has resolved. Use with caution in patients at high infection risk after discussing the relative risks and benefits. Health-care professionals managing patients on mAbs should be aware of the risk of opportunistic infections in patients on mAbs. They should have a high index of suspicion for atypical and opportunistic infections. The mAbs should be promptly stopped in suspected cases and patients should have rapid access to specialist health care for consideration of early anti-bacterial/anti-fungal treatment.	All mAbs
Tuberculosis	Prior to commencing TNFα inhibitors, all patients should be screened for mycobacterial infection Prior to commencing mAbs, consideration of prophylactic anti-mycobacterial therapy should be given to patients with potential latent disease. Patients on mAbs who develop symptoms of mycobacterial infection should receive full anti-mycobacterial chemotherapy but may continue with their mAb if clinically indicated.	All mAbs
HBV and HCV infection	Screening for risk factors for HBV and HCV infection should be performed prior to commencing mAbs and HBV and HCV tests should be performed respectively in patients with risk factors. Close monitoring of LFTs and HBV DNA load or HCV RNA during therapy should be considered in patients with HBV and HCV respectively when treated with mAbs	All mAbs
HIV infection	Risk factors for HIV infection should be documented prior to commencing mAbs and, if present, an HIV test should be done.	All mAbs
Neutropenia	For all patients on mAbs full blood count should be monitored regularly.	All mAbs
Elevation of liver enzymes	LFTs levels should be monitored regularly	All mAbs
Malignancy	Treatment with mAbs may result in increased risk of malignancies. The use of mAbs in patients with pre-existing malignancy is not recommended.	All mAbs

	However, a meta-analysis of clinical registries and prospective observational studies between 1999 and 2010 identified no increase in malignancies, other than skin cancers, including lymphoma, associated with the use of TNFα inhibitors (47)	
Cardiac failure	TNFα inhibitors should not be initiated in patients with NYHA Grade 3 or 4 cardiac failure and should be used with caution in patients with mild (NYHA Grade 1 or 2) cardiac failure. TNFα inhibitors should be discontinued if cardiac failure develops or worsens while on treatment.	TNFα inhibitors
Demyelination	TNFα inhibitors should not be given when there is a clear history of multiple sclerosis and should be used with caution with other demyelinating diseases. TNFα inhibitors should be withdrawn if demyelination occurs and the patient should be referred for specialist investigation.	TNFα inhibitors
Interstitial lung disease	Patients with pre-existing ILD should have monitoring of their lung function if treated with TNFα inhibitors, and consideration should be given to stopping TNFα inhibitors in patients with worsening, or new features of ILD.	TNFα inhibitors
Lupus- like syndrome	If a lupus-like syndrome or other significant auto- immune disease develops, treatment should be discontinued and appropriate interventions should be initiated.	TNFα inhibitors
Psoriasis	If psoriasis develops in patients treated with TNFα inhibitors, conventional psoriasis treatment should be started and consideration should be given to stopping TNFα inhibitors if the skin lesions persist despite specialist dermatology treatment and advice or are particularly severe.	TNFα inhibitors
Diverticular perforation	Tocilizumab and Sarilumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with new onset abdominal symptoms such as persistent pain with fever should be evaluated promptly	Tocilizumab, Sarilumab
Elevations in lipid parameters	Lipid parameters (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides) should be assessed approximately 4 to 8 weeks following initiation of treatment, then at approximately 6 month intervals. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia	Tocilizumab, Sarilumab
Exfoliative dermatitis	Physicians should be alert for symptoms of exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted and Ustekinumab should be discontinued.	Ustekinumab
Progressive multifocal leukoencephalopathy	If neurological symptoms suggestive of PML occur, immunosuppressive treatment should be discontinued and appropriate diagnostic measures initiated.	Abatacept, Rituximab, Belimumab
Depression and suicidality	Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before introduction of treatment and continue to monitor patients during treatment. In patients who experience such symptoms, Belimumab discontinuation should be considered.	Belimumab

Immunoglobulins	oglobulin levels need to be checked regularly, as these can fall following Rituximab treatment and potentially increase the risk of infection.	nab
nonoclonal antibody, NA= Non Applicable, TNF= Tumour Necrosis Factor, HBV= Hepatitis B Virus, HCV= Hepatitis C Virus, LFTs= Liver Function Tests, HIV= Human Immunodeficiency Virus, NYHA= New York Heart Association, ILD= Interstitial Lung Disease, PML= Progressive Multifocal Leukoencephalopathy		

CONCLUSION

Impressive advances in the research associated with better understanding of the aetiopathogenesis of ARDs led to the discovery and therapeutic use of mAbs. These relatively new targeted therapies changed the landscape of treatment in rheumatology, leading to a real progress in achieving a better disease control to patients who had an unmet need through lack or loss of response to cDMARDs or intolerance to these therapies.

As the first biologic treatments have been implemented in clinical use in rheumatology two decades ago, a significant body of evidence is available regarding their safety and efficacy, contributing positively to clinicians and patients' increased confidence in their use. The discovery of biologic treatments led to identification of other numerous potential targets within the inflammatory cascade driving the pathogenesis of various rheumatic diseases which prompted new therapeutic discoveries.

The relative efficacy of newly emerging biologic and non-biologic agents remains to be established through future head-to-head clinical trials which will be required to determine the best and most cost-effective treatment choices for patients. Although having a large number of treatments available is in theory associated with a better chance for achieving optimal disease control, further research is required to facilitate patient personalised treatment approaches for selection of best therapeutic options.

Biologic treatments also offered the prospect of preventing irreversible damage in rheumatic diseases by showing superiority to conventional treatments in multiple clinical trials. In addition, by enabling a rapid control of inflammation associated with ARDs, biologic agents facilitated a re-evaluation of clinical guidelines, which currently focus on early referral, diagnosis and timely treatment optimisation in rheumatic diseases. This subsequently led to the implementation of "treat to target" strategies in inflammatory arthritis and proposal of similar approaches for other ARDs.

The cost implications of biologic treatments can limit patient access to therapy. However, biosimilars offer an exciting opportunity to reduce the cost of treating ARDs. The discovery of new molecules and inflammatory pathways associated with disease inflammation is underway and therefore mAbs will continue to create promising opportunities for the treatment of ARDs.

Further research is still required to identify biomarkers and molecular networks that can help us understand patients' variable response to targeted therapies, as well as how we can better integrate the advanced therapies into the constraints of daily clinical practice for the ongoing benefit of patients and entire society.

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