

Main article

The immune system and new therapies for inflammatory joint disease

Susan M. Oliver RGN MSc

Independent Nurse Specialist, Rheumatology. Member of the Royal College of Nursing Rheumatology Forum Steering Committee.

Abstract

This article provides an overview of the immune system with a specific focus on the role of biologic therapies in treating the consequences of an altered immune response as seen in rheumatoid arthritis (RA). Cytokines are powerful chemical messengers that have a significant role to play in activating an inflammatory response. Two dominant cytokines have been identified as crucial in the inflammatory process that can be seen in RA – tumour necrosis factor alpha (TNF α) and interleukin-1. The term ‘biologic’ is used to describe biologically engineered therapies that are specifically designed to prevent pro-inflammatory cytokines inducing an inflammatory response. Research trials and now clinical practice have clearly demonstrated a significant benefit to patients receiving biologic therapies. The responsibility of the practitioner is to ensure a sound knowledge of biologic therapies, to understand the essential aspects of care and to recognize the importance of guidance documents available to support management and, ultimately, the long-term provision of safe and effective administration of these therapies.

Key words: Biologic therapy, inflammatory joint disease

Introduction

In the last decade research has revealed exciting new insights into the pathophysiology of diseases such as rheumatoid arthritis (RA). This insight has been somewhat of a mixed blessing for health care professionals. As therapies evolve, issues around cost and the selection of appropriate patients are raised and the need for health care resources for rheumatology services increases. Interestingly it has also resulted in the need for practitioners to review their understanding of the immune system in the light of recent research. This is not an

easy quest as often the old tried and tested textbooks are somewhat behind latest innovations, and use terminology that does not reflect the latest research. Any new process or piece of research seems to require new definitions or names to highlight latest understanding or sometimes just to make a claim on a novel new gene or cytokine.

It also needs to be remembered that, with the emergence of these new therapies, further research work will lead to the development of future generations of biologic therapies and treatment options. Although for the purpose of this article the discussion will focus on the use of biologic therapies in RA, a wealth of research continues to examine the benefits of cytokine blocking agents in other autoimmune diseases. For example, spondyloarthropathies, such as psoriatic arthritis and ankylosing spondylitis, have shown promising results with the new therapies (Ritchlin, 2001). This has resulted in new licensed indications: etanercept is licensed for psoriatic arthritis and infliximab is now licensed for ankylosing spondylitis. The use of anti-TNF α blocking therapy (infliximab) has already shown benefit in patients with Crohn's disease and is indicated for the treatment of the severe or fistulizing form of the disease.

Although this paper does not cover specific paediatric aspects of treatment, some of the discussion is relevant to juvenile idiopathic arthritis. However, for more specific aspects of management and assessment for children receiving biologic therapies the reader should refer to key documents (NICE, 2002a; British Paediatric Rheumatology Group, 2000; RCN, 2003).

Research began over a decade ago and as a result of this extensive work the new biologic agents were developed with the potential to block or 'disarm' cell interactions in the early stages of an immune response. These potentially powerful interventions have raised awareness of many auto-immune diseases and raised expectations that in the next decade there will be more effective treatments for them.

There are two specific cytokines that have undergone extensive research in this area, tumour necrosis factor alpha (TNF α) and interleukin-1 receptor antagonist. These two cytokines play an active role in the normal inflammatory response. The role of these new cytokine blocking agents (anakinra, etanercept, infliximab) are addressed in the treatment of RA. Adalimumab is discussed briefly. Although data have been presented on the early results of research trials on adalimumab at the time of going to press it is not yet licensed for the treatment of RA. Two of these therapies have been reviewed by the National Institute of Clinical Excellence (NICE) and are licensed for the treatment of RA. They are infliximab and etanercept (NICE, 2002b). Etanercept is also licensed in the treatment juvenile idiopathic arthritis (JIA).

The discussion in this article focuses on the mechanisms involved in auto-

immune disease and the new therapeutic agents developed to target specifically the early process of an immune response. The paper discusses:

- An overview of the immune system and auto-immune disease
- An explanation of the role of cytokines and immunoglobulins in auto-immune disease
- An explanation of the action of the new targeted therapies in RA

The immune response

The function of the immune system is to protect the body from attack or damage caused by micro-organisms. These micro-organisms could be bacteria, viruses, fungi or parasites. The immune system is a vast and fascinating topic with a range of cells playing an active part in protecting the body from damage. In the past we were taught that there were two types of immune mechanisms; the innate, otherwise called natural immunity, and the acquired, also called adaptive immunity (Table 1). Although these two types of immune response appear clear-cut and separate there are significant aspects of an immune response that are inter-related. Natural immunity is a non-specific rapid response and is not dependent on the body identifying the specific foreign organisms. Adaptive immunity is highly specific, relying on the body's ability to recognize the 'invader' and launch a targeted response based upon clear recognition of the make up of the organism.

Natural (innate) immunity prevents entry of micro-organisms into tissues using mechanical barriers, skin surfaces, mucous membranes and antibacterial substances in secretions. It does not become more efficient on repeated exposure but responds in the same way to all micro-organisms. Other aspects of this response occur by phagocytosis (the ingestion and killing of micro-organisms by specialist T-cells called phagocytes). The response is usually localized, such as a break in the skin resulting in a routine inflammatory response to micro-organisms breaking the normal immune barrier.

Acquired (adaptive) immunity is based upon the memory of the immune system and the ability to recognize previous invaders. Acquired immunity means that body has the ability to recognize micro-organisms that have previously 'invaded' the body and the normal result would be a 'specific and targeted response' to the invader. This system relies upon the body recognizing 'self' and 'non-self' or invader cells.

Understanding auto-immune disease and immunoglobulins

There is now a greater understanding of the complex cell interactions that enable us to have an efficient immune system. In the last decade research has focused on a clearer understanding of immune responses and this has revealed new treatments that are more specifically 'designed' to target key components in the immune process.

Table 1: Acquired and active immunity	
Acquired (adaptive) immunity	Active (innate) immunity
Requires immune system 'memory' Response slower than active immunity but specific target attack based upon previous exposure to antigen	Normal protective immune mechanisms Response does not alter despite repeated 'attacks'
<ul style="list-style-type: none"> ● Immunity based upon previous exposure ● Immunological recognition (antigen recognition) ● Discriminates between self and non-self ● Specific target response – recognize as foreign micro-organism/antigen ● Reacts to 'invaders' by the production of specific antibodies (immunoglobulins) ● Cellular basis of immune response – lymphocytes – T-cells and B-cells ● Phagocytes also act on cell-mediated responses ingesting antigen and breaking it down ● Macrophages or lymphocytes present antigen to T-cells and B-cells 	<ul style="list-style-type: none"> ● Specific human immunity – present at birth (natural immunity to other species diseases, e.g. cowpox) ● Genetic predisposition to some diseases, e.g. cystic fibrosis ● Skin, mucous membranes ● Antibacterial secretions – tears, saliva ● Ciliary activity – upward flow of secretions – bronchial tree ● Coughing, vomiting ● Skin – broken skin results in increased blood supply, increased capillary permeability allowing pooling of tissues and non-specific ingestion of antigens (phagocytosis)

A number of chronic illnesses are known to have an auto-immune component resulting in the self-destruction of vital tissues. The consequences of the disease will depend on what tissues are damaged as a result of the body's 'malfunction'.

One good example of an auto-immune disease is RA. In RA an abnormal immune response is 'triggered' by the immune systems' faulty recognition of the 'self' molecules such as immunoglobulin G. Similar responses are seen in other 'faulty' immune responses, for example the immune system of a patient with diabetes mellitus recognizes pancreatic cells as 'foreign' and as a result 'triggers' an immune response that causes cell damage to the pancreas.

To understand immunity it is useful to think of the immune system working as an army (Isenberg and Morrow, 1995). An antigen is a foreign substance that invades the body. The body's response to antigens or 'foreign' invaders is to launch a response from lymphocytes. Lymphocytes are specific white blood cells that originate and develop in bone marrow and are initially called stem cells. These stem cells are similar to new young army recruits, and the bone marrow can be thought of as the headquarters and recruitment centre. Some of the young stem cells are developed and trained as general soldiers, called B-lymphocyte cells, and are sent to

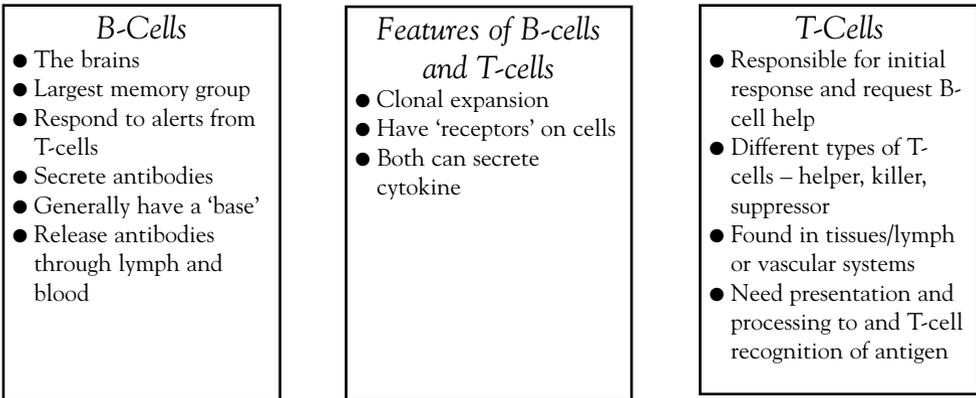


Figure 1: The key players.

base camps around the body. The base camps are situated in lymphoid tissue in the tonsils, adenoids, lymph nodes, spleen, lymphatic vessels and patches of lymphoid tissue in the intestines.

The system is very efficient with good communication between different areas (base camps) of lymphoid tissue, using the lymphatic system as an efficient means of travel. (One quarter of all developed T-lymphocytes are present in lymphoid tissues.)

Some of these stem cells are sent to train as specialist T-cells in the thymus gland. The thymus is also lymphoid tissue and could be thought of as an 'elite' training camp. Stem cells from here are called T-lymphocyte cells.

Although T-cells and B-cells have their own unique roles in arming the immune system they also have some common characteristics (Figure 1). Both T- and B-cells are capable of 'clonal expansion', that is the ability to reproduce themselves rapidly when needed. They have 'receptors' that enable good communication and contact with antigens (foreign invaders). Another important role of lymphocytes is the ability to secrete potent chemical messengers (cytokines) that trigger a response from other cells, particularly in response to a 'foreign invader' or antigen. Cytokines can be secreted by T- or B-cells although this is predominantly the role of T-cells. A clear difference between the two cells is that T-cells need antigens to be 'presented' to them in a specific way by other cells.

A T-cell will identify an antigen when an antigen presenting cell (APC) comes into contact with it and presents an antigen to it. The antigen is carried within the binding groove of a major histocompatibility complex (MHC) molecule which is transported to the surface of the APC. For the purpose of this discussion detailed explanations of MHC will not be given but it is important to understand that antigen presentation by the MHC system is essential in alerting the lymphocyte cells to launch an appropriate attack.

Examples of APCs are B-cells and macrophages. One of the most significant

roles of macrophages is to work as APCs although they play numerous roles as part of the immune army. Macrophages are distributed throughout the body in tissues and blood and have the potential to consume passing antigens and immune complexes by cleaning up debris throughout the body's immune system. This ability is one of phagocytosis and other cells in the immune system can also undertake this role. When the macrophage works as an APC it uses enzymes to partially break down the proteins in the antigen to smaller peptides before presenting these to the T-cells.

The role of the APC and how it presents the antigen to the T-cell will also influence the type of response it will make to the antigen (the army's attack response). This is a complex process but the chief point to remember is that a T-cell can launch a different response depending on the antigen presented. The MHC is also referred to in humans as human leucocyte antigen (HLA). The HLA system determines which antigens are recognized by an individual and vary from person to person. RA is strongly linked to the HLA-DRB1 region of the MHC Class II complex. This complex association continues to be an area of interest in research into identifying the cause and process involved in auto-immune disease. Molecules of the MHC Class II complex present the antigen to T-helper cells. The activation of T-helper cells with a specific marker on them (called CD4) induces a cytokine response as well as an antibody response from the B-cells (Choy and Panayi, 2001). Although there are other immune cells in this response it is important for this discussion to focus on the T-helper cell.

The response the T-cell launches will be in the form of a powerful cytokine or chemical messenger. Monocytes, macrophages, fibroblasts and T-cells can release numerous cytokines on stimulation. Each cytokine has a specific role within the immune system. Such roles can include inducing acute phase response, increasing cell adhesion and cell growth and increasing the production of destructive enzymes in RA.

The cytokine or messenger can be released in the blood or lymphatic system. When the cytokine is released it needs to 'lock into' a cytokine receptor. Once it is locked into a receptor it can launch a number of responses.

B-lymphocyte cells, although less highly specialized, are the memory of the immune system. B-cells can be thought of as the intelligence corp of an army and as mentioned earlier are mainly based in the lymphoid tissues around the body. They have the ability to remember many previous antigens (foreign invaders) and have a tailor-made immune response that can destroy them. B-cells will respond quickly to requests from T-cells when they recognize the initial attack from an antigen. The B-cell memory results in a tailor-made decisive 'bullet' or attack on the antigen released through the lymphatic or blood system. This tailor-made response is an immunoglobulin (antibody). An immunoglobulin is almost always a 'Y'-shape cell structure (see Figure 2).

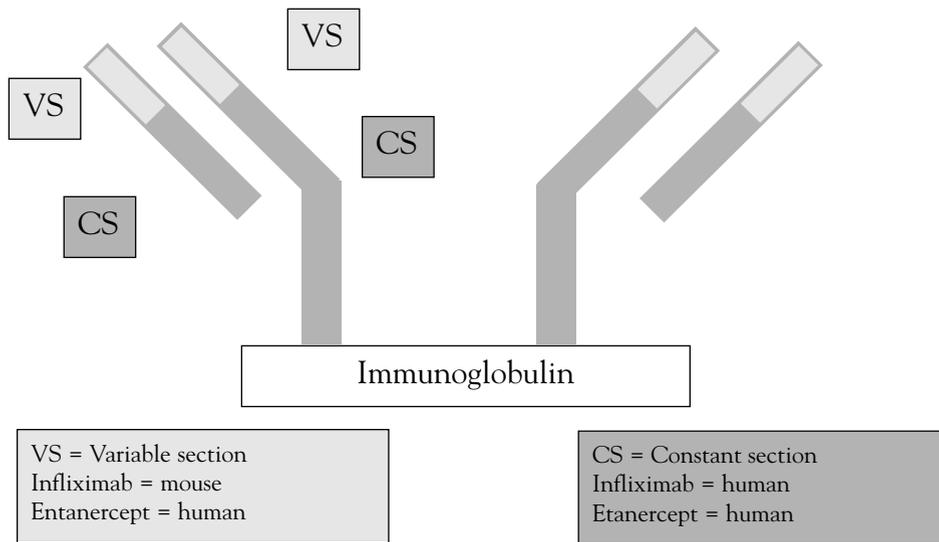


Figure 2: Immunoglobulin showing variable and constant portion of structure.

The significance of the Y shape is essential in understanding some of the new treatments that aim to control auto-immune disease. The shape of an immunoglobulin is based upon the Y having one section of its shape that is 'constant' and one section that is 'flexible' (i.e. changeable). The V, or top part of the Y shape, is the flexible portion that can be manipulated in the laboratory. The V section is where the antigen sticks when it is trapped by the immunoglobulin. To understand this further we need to focus upon the normal mechanism of the immunoglobulin.

When a B-cell recognizes an antigen it sends out an immunoglobulin specifically made to match that antigen. The immunoglobulin has a specific portion on the V part of the Y that recognizes the shape of the antigen. This acts like a lock and key (Figure 3). The region on the antigen recognized by the immunoglobulin is called an epitope. Many different potential antibody-producing B-cells pre-exist in the body, each having the ability to make an antibody of a different specificity. On binding antigen, the cell is activated to divide and produce identical cells, producing identical antibodies to the specific antigens.

It is now possible to see that both T-cells and B-cells are essential in the normal immune response. Recalling that the T-helper cell needs to have a specific antigen presented to it by an APC we can now clarify the chain of events in RA. One theory is that at some point an antigen response is made against a foreign or self-protein which triggers an inflammatory cascade. The particular antigen involved has not been identified. It could be a foreign antigen such as a bacterium

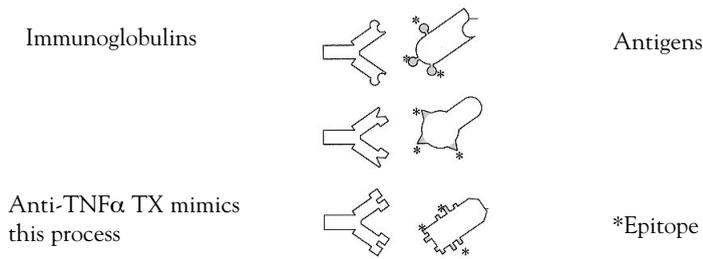


Figure 3: Antigens and immunoglobulins.

or virus, or a self-antigen such as collagen or IgG. Antigen is broken down into small peptide fragments within APCs before becoming bound to MHC Class II molecules. Only certain peptides will bind to MHC Class II molecules. This depends on the particular form of the MHC Class II molecule and the size and amino acid sequence of the peptide fragments. MHC Class II genes exist as many different variants. Certain individuals with particular MHC Class II variants are more susceptible to RA. All MHC Class II modules associated with RA have a common region where they bind to antigenic peptides. This has led to the suggestion that these particular MHC variants bind and present a peptide which is able to trigger RA.

Anti-TNF α and interleukin-1

The normal activated immune response to inflammation is to launch various pro-inflammatory cytokines. Two of the most significant cytokines involved in instigating an inflammatory response are TNF α and interleukin-1 (IL-1). These cytokines need to lock onto specific receptors on the surface of cells such as those in synovial tissue. The receptor activation results in a burst of activity from such cells, with release of cytokines and other inflammatory mediators causing various processes in the body to respond to the attack. This response is called the inflammatory cascade (see Figure 4).

Although there are some differences in the specific mechanisms of action in anti-TNF α therapies (etanercept, infliximab and adalimumab) and IL-1 receptor antagonist (anakinra), the important aspect to remember is that the normal activation process is stopped by blocking the cytokines' ability to connect to their cell surface receptors.

However, it is important to clarify the role of the cytokine TNF α in one additional respect. As the name implies tumour necrosis factor alpha has a role in causing death or necrosis of malignant or pre-malignant T-cells within the body.

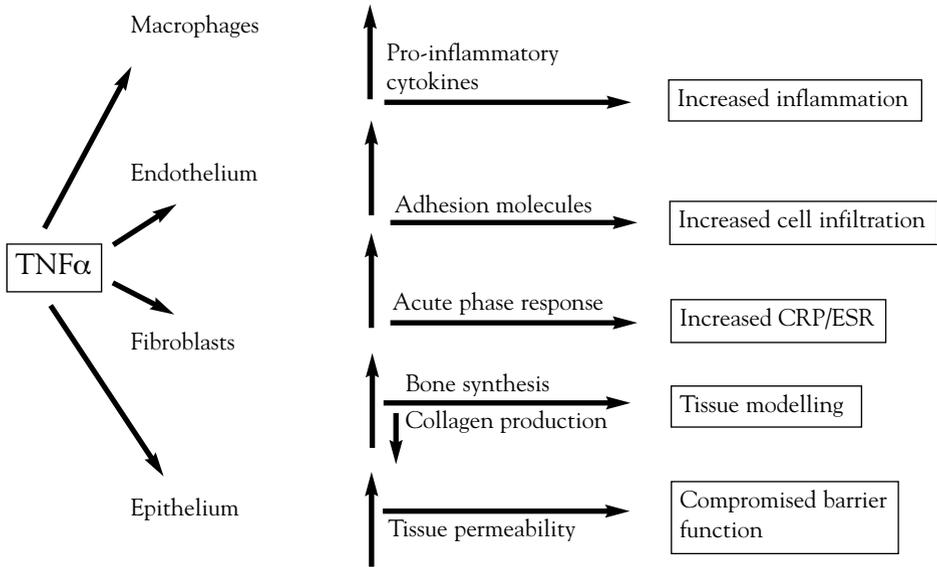


Figure 4: Inflammatory cascade. Reproduced by kind permission of Schering Plough Ltd.

Blocking this process has the theoretical possibility of allowing malignant or pre-malignant T-cells to develop. To date, the clinical evidence has not demonstrated any differences between patients with RA who have received traditional therapies and patients receiving anti- $TNF\alpha$ treatments. Patients with RA have an increased risk of developing a malignancy partly due to their aggressive disease but also as a result of other toxic therapies they receive (Pincus and Callahan, 1993; Abu Shakra et al., 2001).

Anakinra is a recombinant form of the human IL-1 receptor antagonist (IL-1Ra), an anti-inflammatory cytokine. Anakinra actively competes with IL-1, locking into the receptor and thus disarming the potential of IL-1 (a pro-inflammatory cytokine) to activate an inflammatory response. IL-1Ra is present in the body normally but it is thought that patients with inflammatory joint disease have relatively low naturally occurring amounts of IL-1Ra while the amount of IL-1 is high. This means that more IL-1 cytokine molecules are able to lock into the receptors resulting in an inflammatory response (Jiang et al., 2000)

Immunosuppression

Many of the therapeutic options used in suppressing RA have also been used in other auto-immune diseases. Extensive research continues to investigate the value of identifying and targeting specific cytokines thought to have an active

role in activating the immune response in the hope of ‘blocking’ or ‘disarming’ this response.

Immunosuppressive therapies have evolved, sometimes without a clear understanding of the mechanisms that reduce the immune response. The use of these agents, which have some effect on controlling the disease process, are not without a range of serious side effects and yet still fail to suppress adequately the auto-immune disease.

Targeted therapies – an overview

The recognition of TNF α and its role in the inflammatory cascade led research to focus on the development of an antibody to lock into or block the cytokine from connecting to its cell surface receptors. New biologic therapies have resulted from this research. The focus in developing these therapies has been on two specific cytokines implicated in instigating the inflammatory cascade: TNF α and IL-1.

Etanercept, infliximab and adalimumab

The anti-TNF α drugs, infliximab and etanercept have been developed along these principles and are now available for the treatment of active RA. Adalimumab is a new anti-TNF α therapy but it is not yet licensed in the UK. Two of these therapies (etanercept and infliximab) have been approved by the National Institute of Clinical Excellence (NICE, 2002a). There are differences between infliximab and etanercept. Infliximab is an engineered antibody against TNF α , blocking soluble and tissue-bound receptors, whereas etanercept is an engineered soluble receptor molecule (i.e. p75) which interferes with binding of TNF α to its cell bound receptor.

Biologic therapies have demonstrated significant symptomatic benefit to approximately 70% of patients receiving treatment (Emery et al., 1999). Symptomatic relief is important, but an essential aspect of care is that of maintaining functional ability by reducing erosions to the joints and the subsequent loss of joint space. It has been suggested that reduction in joint erosion and joint space narrowing continues even in some patients who fail to gain symptomatic relief (Lipsky et al., 2000).

Adalimumab is a human anti-TNF α treatment that blocks soluble and tissue-bound receptors. Early data appear promising.

Anakinra

Anakinra is an IL-1 receptor antagonist blocking agent. Anakinra works on selectively or partially blocking IL-1. IL-1 is a cytokine implicated in the inflammatory cascade and the subsequent mechanisms that lead to progressive joint destruction in RA. Early data suggest it produces a reduction in the rate of joint erosion and the signs and symptoms of RA (Bresnihan, 2001).

Table 2: Biologic therapies			
Adalimumab Anti-TNF α	Anakinra IL-1Ra	Etanercept Anti-TNF α	Infliximab Anti-TNF α
Treatment of RA		Treatment of adult RA and PSA	Treatment of RA
<i>Dosage</i> 20–40 mg 1–2 weekly (data awaited)	100 mg daily	25 mg twice weekly JIA: 0.4 mg/kg body weight (max 25 mg dose)	RA: 3 mg/kg of body weight AS: 5 mg/kg of body weight
<i>Additional medication</i> Data awaited	Administer with methotrexate	None	Administer with methotrexate
<i>Administration</i> Fortnightly or weekly subcutaneous injection	Daily subcutaneous injection	Twice weekly subcutaneous injection	IV infusions at 0, 2, 6 weeks and then 8 weekly
<i>Elimination half-life</i> 10–18 days	4–6 hours	70 hours	Approx 8 weeks post-infusion
<i>Licensing</i> Preliminary information only based on research data. Licensed indication for RA in Europe, no license in UK	Reviewed by NICE, final reported awaited	Licensed indications for RA, JIA and PSA	Licensed indications for RA, Crohn's severe and fistulizing and AS*
<i>Blood monitoring</i> Data awaited	As for methotrexate	None stipulated	As for methotrexate
*For details of dosages and treatment regimes see Summary of Product Characteristics (SPC) sheets available at www.emc.vhn.net . For additional information refer to the RCN (2003) Guidance for practitioners on the assessment, management and administration of biologic therapies RA: rheumatoid arthritis, PSA: psoriatic arthritis; JIA: juvenile psoriatic arthritis; AS: ankylosing spondylitis			

Practical issues in biologic therapies

It is important to understand the underlying theoretical issues of the immune system and to relate this information to how best to care for patients receiving these treatments. So what are the key issues for practitioners?

There is now a wealth of research and clinical data on patients receiving biologic therapies. Yet, this is a new and evolving area. The length and mechanism of action, route of administration, monitoring requirements and need for concomitant medications (such as methotrexate) vary with each of these drugs.

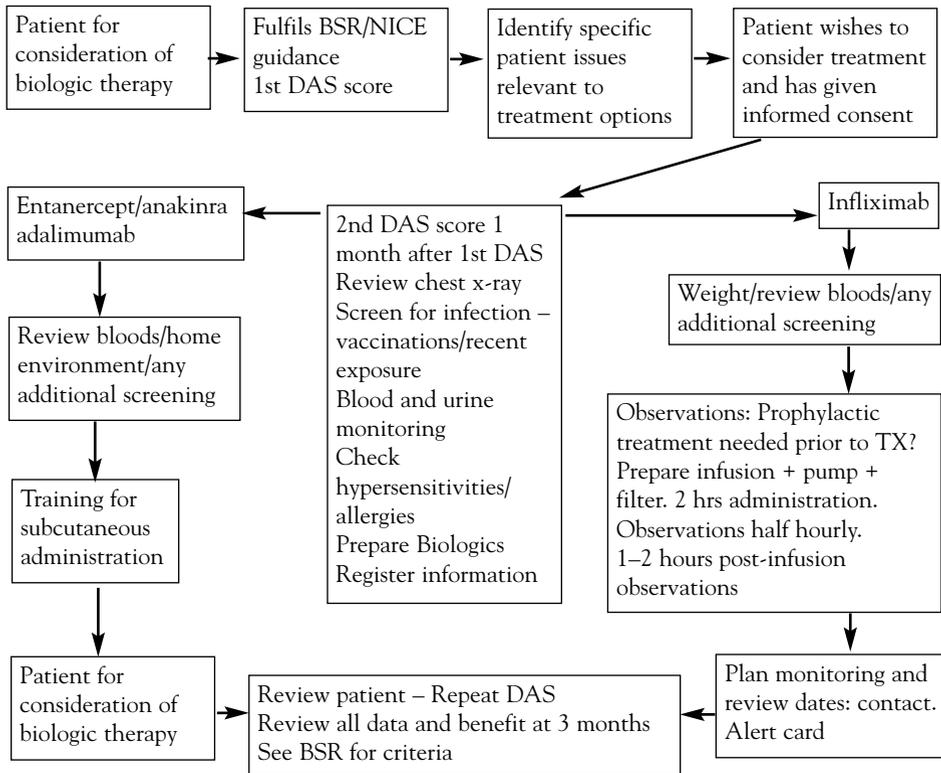


Figure 5: Flow chart for the management of a patient on biologics.

However, there are key concepts that the practitioner needs to apply for all patients receiving biologic therapies. These include detailed and thorough counselling to ensure the patient has consented to treatment. The patient should be prepared appropriately and screened prior to starting treatment. Screening should not only include clinical data such as routine observations and blood results but also ensure that the patient is free from any long-standing or current infections. Table 2 and Figure 5 set out some basic information on the administration of these therapies. For a detailed stepwise approach to caring for patients on biologic therapies refer to the Royal College of Nursing Guidance document for practitioners (RCN, 2003)

All practitioners should carry out a joint assessment using the Disease Activity Score (DAS). In Europe the DAS, using a 28-joint count, has been recognized as the measure of choice in clinical practice to assess benefit of treatment. The European League Against Rheumatism (EULAR) 28-joint count has been validated for use in a clinical setting (Scott et al., 1995)

A detailed explanation of the exclusion and inclusion criteria for patients receiving anti-TNF α treatments can be found in the document prepared by the British Society of Rheumatology (2000). This document, and the criteria set out, form part of the NICE guidance on administration of etanercept and infliximab for adults with RA. An additional document is available for children with juvenile idiopathic arthritis receiving etanercept (NICE, 2002a, British Paediatric Rheumatology Group, 2000).

It is clear, from an understanding of the mechanisms of action of biologic therapies, that blocking the normal inflammatory response may have potential risks of infections or re-emergence of latent infections such as tuberculosis or other previous longstanding infections. Equally, sensitivity reactions vary with each of these drugs and practitioners need to be vigilant when administering treatment. It is good practice to ensure that practitioners supporting patients on these therapies are competent and conversant with their local policy on anaphylaxis treatment, emergency resuscitation and management of intravenous infusions. It may be necessary to review competencies on subcutaneous administration techniques and any policy required to teach patients to self-administer therapies if pharmaceutical support services are not being used.

It is not possible within the scope of this article to discuss in detail the role of the practitioner and the risks and benefits of biologic therapies. This information can be found in the Royal College of Nursing's guidance for practitioners in the assessment, management and administration of biologic therapies. This guidance can be accessed via the Royal College of Nursing website. It is hoped this work will provide a framework for practice and guide individual practitioners caring for patients receiving these therapies

It is important to ensure effective screening prior to treatment. This should include checking for signs of infection and vigilance if a patient complains of new symptoms such as respiratory, cardiac or neurological problems. Patients should always be provided with details of their treatment and encouraged to report early any deterioration in their general health. A contact number should be provided with advice about using the on-call service.

As informed practitioners there is a responsibility to ensure that knowledge, competencies and skills are used appropriately to support patients receiving biologic therapies. Good data collection and collaboration with the BSR Biologics Register is an integral part of the management process. The review by NICE in 2006 will rely heavily on the data collected from the Biologics Register and local audits. A thorough and safe assessment process, together with adequate resources to assess, manage, train and administer biologic therapies will be imperative in the next few years.

The future looks promising for patients with inflammatory joint disease. Practitioners need to plan for future provision, not only in basic resources, but in training expert practitioners in this evolving and dynamic area of care.

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Correspondence should be sent to Susan Oliver, Independent Rheumatology Nurse Specialist, 7 Trafalgar Lawn, Barnstaple, N Devon EX32 4JB. Email: susan.oliver@bigfoot.com