There have been many exciting developments in rheumatology over the last two decades. A greater understanding of the functioning of the immune system in rheumatologic disorders has resulted in the development of targeted biologic therapies for patients. Biologic therapies represent a new kind of treatment for patients with a wide range of rheumatologic conditions such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and systemic lupus erythematosus (SLE). Traditional therapies such as methotrexate, salazopyrine, plaquenil and arava are still very much part of the patients prescribed program with methotrexate remaining the first line treatment used in the management of inflammatory arthritis. However the advances in molecular biology have led to an array of new treatment approaches to inflammatory arthritis. How do these biologic therapies work? Biologic therapies target the abnormal functioning immune system. Some target the immune cells-regulating cytokine production, others work by targeting the cytokines.

What are cytokines and why are they important? Cytokines are a group of proteins that play a role in cell signaling. They are produced by immune cells (T and B cells). Cytokines interact with cells of the immune system in order to regulate the body’s response to disease and infection. Cytokines are important mediators of the immune response. Where there is an overproduction of cytokines or an inappropriate amount of cytokines produced, disease can occur. Examples of cytokines that play a lead role in inflammatory arthritis are interleukin-1 (IL-1), interleukin-6 (IL-6) and TNF-alpha. Overproduction of multiple cytokines results in inflammation, which over time leads to bone erosion and damage to the joints. What does this mean for patients with rheumatologic conditions? There are now a variety of treatments available that target indi-
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**Safety concerns**

Like all immunosuppressive treatments, biologic therapies pose an increased risk of infections and other side effects. The EULAR (European League against Rheumatism) guidelines recommend that all patients commencing biologic therapies should be screened for latent or active TB, hepatitis B and herpes zoster and receive immunisation against herpes zoster (if required) alongside influenza and pneumococcal.

Bacterial infections and opportunistic infections such as listeria, herpes related viruses and tuberculosis have been reported with the use of biologic agents. The reactivation of latent TB has led to the introduction of pre-treatment screening which includes a CXR and a quantiferon test or Mantoux test prior to treatment.

Injection site reactions have also been well documented. One in ten patients gets severe reactions where treatment is ceased immediately. Most injection site reactions reported are mild localised reactions that improve within a short period of time. Infusions such as rituximab and infliximab deliver high serum concentrations and as a result can cause infusion related reactions. Changes in a patient’s blood pressure, heart rate and temperature have been reported with other patients experiencing shortness of breath, rash, headaches and nausea.

Patients are discouraged from having live vaccines whilst on treatment. Live vaccinations can trigger the symptoms of the disease so are therefore not recommended and patients are advised not to travel to countries requiring yellow fever or polio vaccines for example. This is in keeping with EULAR (European League against Rheumatism) guidelines. The reactivation of latent TB has led to the introduction of pre-treatment screening which includes a CXR and a quantiferon test or Mantoux test prior to treatment.

In rheumatology, B cell depletion therapy is used for the treatment of RA, SLE and vasculitis. Rituximab is used for the treatment of RA in anti-TNF non-responders. The role of B cells in the pathogenesis of RA is not fully understood but clinical studies demonstrate that rituximab can be effective in up to 50 per cent of anti-TNF non-responders. B cells are essential to the development of SLE and vasculitis. B cells produce harmful antibodies that may attack the body’s own tissues. Rituximab depletes these cells in order to gain good disease control. Rituximab is an infusion administered usually twice yearly with a two week gap between each cycle.

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increased risk of NMSC (non-melanoma skin cancer). It is important that a previous history of melanoma is excluded prior to commencing treatment and patients are educated on skin cancer prevention.

It is imperative that patients on biologic therapies attend their clinic appointments as scheduled. Most biologic patients are on the traditional disease modifying drugs and therefore attend their hospital or GP for regular blood monitoring to assess for any renal, liver or blood count abnormalities. Even patients on monotherapy need to attend for regular blood monitoring. Every country and even every centre does things differently but certainly the rule of thumb would be every eight weeks at least. Regular reviews within the first twelve months of treatment with both the nursing and medical team are essential to observe for any side effects of treatment and more importantly to assess for good disease control. 6-10

Pregnancy

Some traditional therapies, methotrexate being one, are contraindicated in women or men planning a pregnancy. Methotrexate is a teratogenic drug causing foetal abnormalities and miscarriage.5,10 Patients are therefore advised to remain off methotrexate for six months prior to conceiving (female) and three months (male) and during breastfeeding.

Information on the newer biologic therapies is hard to obtain as there are no clinical trials involving pregnant women. The pharmaceutical producers of anti-TNF agents advise against continuing treatment prior to a planned pregnancy. Increasingly reports of both planned and unplanned pregnancies with patients remaining on biologic therapies during pregnancy have been noted. A review of the literature examining anti-TNF agents during pregnancy revealed that there was no increase in miscarriage, pre-term birth or deformities compared to untreated healthy pregnant controls. 5,14 The current UK guidelines state that with the exception of etanercept, all other anti-TNF agents should be discontinued 5–6 months before conception. 11 Etanercept, because of its short half-life can be discontinued 3 weeks prior to conception. Cetolizumab is not thought to cross the placenta and therefore may be a treatment option for a patient planning a pregnancy, although there have been studies reporting low levels of the drug in newborns.12 Studies of women on infliximab and adalimumab showed drug levels in the newborn and within the first few weeks of life are the equivalent to that of their mother. Etanercept drug levels have been found in the newborn although these were a considerably reduced portion of the levels found in the mother’s circulation. 12 This would indicate a less significant amount of active transport of this antibody. Overall the evidence of using anti-TNF therapies in pregnancy suggests that there is no adverse effect of exposure to anti-TNF agents at conception although the long-term effects of monoclonal antibodies such as infliximab and adalimumab are not yet known. 11,12

Data on rituximab during pregnancy is limited. It is known that rituximab crosses the placenta from week 16. There is clinical evidence that rituximab, when dispensed during the second and third trimester, can cause B-cell depletion in the foetus. 13 It is therefore recommended that if used during a planned pregnancy, maternal serum levels should be checked prior to conceiving and only if serum levels are negative should conceiving commence.

There has been limited evidence to date of abatacept used during pregnancy. Abatacept crosses the placenta. It is recommended that abatacept should be avoided in patients planning or during a pregnancy. 11,12

To date there have been no human pregnancy studies using ustekinumab or tocilizumab, therefore treatment should be avoided in patients planning or during a pregnancy. 11,12

Summary

Targeted biological therapies have provided significant benefits over traditional therapies and represent a significant advancement in the treatment of rheumatologic conditions. Biologic therapies have revolutionised the world of rheumatology. Advances in biologic agents have given both patients and clinicians increased options for effective disease management, but like all immunosuppressive therapies caution is required. Careful pre-treatment screening and monitoring of patients on biologic therapy is essential. The growing evidence that anti-TNF agents show no adverse effects to the foetus at the time of conception is positive, although the long-term effects of monoclonal antibodies is unknown. The use of other biologic therapies in pregnancy remains limited and therefore their use cannot be recommended at this time.

References