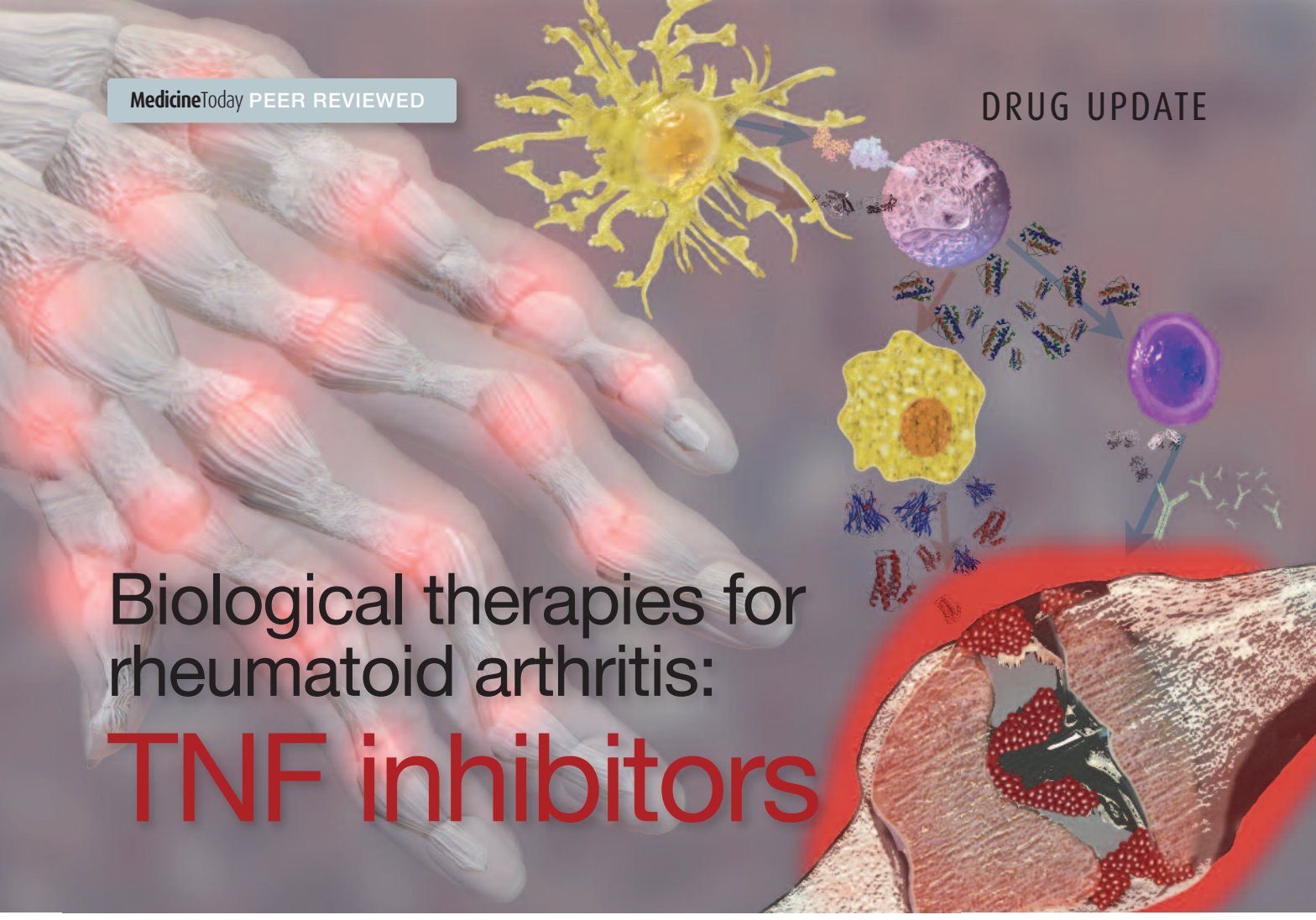

Biological therapies for rheumatoid arthritis: TNF inhibitors

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The advent of TNF inhibitors represents a significant advance in treatment options for patients with rheumatoid arthritis who are refractory to traditional DMARD therapy.

MedicineToday 2011; 12(10): 87-92

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder of unknown aetiology. It is the most common form of inflammatory arthritis and affects about 0.5 to 1% of the adult population worldwide.[1-4] The peak incidence of disease onset occurs in people aged between 20 and 40 years, with women representing three-quarters of all those diagnosed with the condition.[2,5]

RA is characterised by a symmetrical polyarthritis and morning stiffness that persists beyond six weeks' duration.[6,7] Untreated, RA causes progressive, irreversible, erosive joint damage and deformity. This, in turn, leads to disability, early loss of work productivity and reduced life expectancy by an average of about 10 years.[1,2,5,8]

The goal of treatment for patients with RA is to induce complete disease remission by controlling the underlying inflammatory process. This requires early diagnosis and timely initiation of disease-modifying antirheumatic drugs (DMARDs). Methotrexate, a traditional DMARD, is the most commonly prescribed first-line agent, and remains the cornerstone of combination DMARD therapy.[9-11]

Although traditional DMARD therapies are effective for a large proportion of patients, some individuals continue to experience inadequate disease control. The new biological DMARDs represent a significant advance in treatment options, allowing an additional percentage of patients with active RA to achieve good disease control.

TARGETING RA WITH BIOLOGICAL THERAPIES

Biological therapies for RA are DMARDs designed to inhibit specific components of the immune system, particularly cytokines, which play a key role in promoting inflammation.

TABLE. TNF INHIBITORS CURRENTLY AVAILABLE ON THE PBS[14]

TNF inhibitor	Route of administration	Mechanism of action	Use in pregnancy: drug category
Infliximab	Intravenous infusion of 3 mg/kg at 0, 2 and 6 weeks, and every 8 weeks thereafter, in combination with methotrexate	Chimeric human–murine monoclonal antibody to TNFα	C
Etanercept	Subcutaneous injection of either 25 mg twice weekly or 50 mg once weekly	Recombinant monoclonal soluble TNF receptor that binds TNFα	B2
Adalimumab	Subcutaneous injection of 40 mg every 2 weeks	Recombinant fully humanised monoclonal antibody to TNFα	C
Golimumab	Subcutaneous injection of 50 to 100 mg every 4 weeks, in combination with methotrexate	Fully humanised monoclonal antibody to TNFα	C
Certolizumab pegol	Subcutaneous injection of 400 mg every 2 weeks for the first three doses, then every 4 weeks thereafter	PEGylated humanised monoclonal antibody to TNFα	C

ABBREVIATION: TNF = tumour necrosis factor.

Biological DMARDs have a faster onset of action compared with traditional DMARDs. However, predominantly for cost reasons, they are usually reserved for use in patients with a suboptimal treatment response, or in those who are intolerant to traditional DMARDs.[12,13] Conventional DMARDs, such as methotrexate, remain the first-line treatment for RA.

There are two general classes of biological DMARDs available for the treatment of patients with RA and these are:

- tumour necrosis factor (TNF) inhibitors (Table), of which there are two major types:
  - soluble TNF receptors (e.g. etanercept)
  - monoclonal antibodies against TNFα (e.g. infliximab, adalimumab, golimumab and certolizumab pegol).
- non-TNF inhibitors (e.g. abatacept, tocilizumab and rituximab).[5]

This article focuses on the TNF inhibitors.

INTRODUCING TNF INHIBITORS

TNF inhibitors are the most widely used biological DMARDs for the treatment of patients with severe RA.[15]

There are five TNF inhibitors currently available for clinical use on the PBS:

- infliximab
- etanercept
- adalimumab
- golimumab
- certolizumab pegol.

Why do TNF inhibitors work in RA?

TNF inhibitors work by blocking activation of TNFα, a pro-inflammatory cytokine released by activated immune cells. TNFα is an important constituent of the immune response to infection and is upregulated in the synovium of patients with active RA.[14] The cytokine acts synergistically to induce the release of matrix metalloproteinases and receptor activation of nuclear factor-κB ligand (RANKL), causing cartilage degradation and bone erosion (via osteoclast activation).[16]

Antagonism of TNFα – for example, with TNF inhibitors – suppresses synovitis and almost completely eradicates bone and joint destruction.

How effective are TNF inhibitors in RA?

Randomised studies demonstrate similar efficacy between methotrexate and TNF inhibitors in the initial treatment of patients with RA. However, TNF inhibitors have been shown to work in patients who respond inadequately to conventional DMARDs, particularly when used in combination with methotrexate.

Clinical response rates of up to two-thirds have been reported in patients with RA treated with TNF inhibitors.[17] Significant improvements in function, quality of life and prevention of radiographic progression have been demonstrated with their use in patients with severe RA.[18]

Although differing in molecular structure, pharmacokinetics and dosing regimens (Table), the currently available TNF inhibitors display similar therapeutic and safety profiles.[5,19] Clinical trials suggest all five PBS-listed TNF inhibitors are equally effective, especially when used in combination with methotrexate.[20]

About a third of patients do not appear to respond to initial TNF inhibitor therapy. In such cases, switching to a second TNF inhibitor or switching to a non-TNF

inhibitor biological agent, irrespective of the reason for discontinuation of the first agent, is an effective alternative therapeutic option.[17,20]

Who can prescribe TNF inhibitors and what are the PBS guidelines?

In Australia, the prescribing of TNF inhibitors for the treatment of patients with RA is currently restricted to rheumatologists and clinical immunologists. New PBS guidelines pertaining to the prescription of TNF inhibitors took effect from 1 August 2010. One of the key changes to the PBS criteria affects patient eligibility, and states that patients must fail at least six months of intensive treatment with traditional DMARDS before being prescribed a TNF inhibitor. Treatment with traditional DMARDs includes three months or longer of continuous treatment with at least two DMARDs, which must include:

- methotrexate (≥ 20 mg weekly); and
- two of hydroxychloroquine (≥ 200 mg daily), leflunomide (≥ 10 mg daily) or sulfasalazine (≥ 2 g daily).

Full prescribing information is available on the Medicare Australia website at www.medicareaustralia.gov.au.

TNF inhibitors work best in patients with early RA compared with in those with long-standing RA. Conventional DMARD therapy should thus be implemented early to establish as quickly as possible which patients demonstrate an inadequate response to treatment, and in whom it is appropriate to consider the use of TNF inhibitors.

What needs monitoring?

No formal recommendations currently exist with regard to the routine monitoring of patients taking TNF inhibitors. Early recognition of occult sepsis (especially opportunistic fungal infections) and prompt institution of appropriate antimicrobial therapy is advised.[14]

Patients taking TNF inhibitors, particularly when taking them in combination with corticosteroids, often do not present with the typical symptoms (e.g. fever) that usually accompany infection. In the event of nonresolving infections, and after consultation with the patient's treating rheumatologist, the TNF inhibitors should be discontinued until the patient recovers from the infection.

What are the common side effects?

Infusion and injection site reactions are among the most common adverse effects reported.[21] Injection site erythema and swelling caused by subcutaneous preparations of TNF inhibitors (etanercept, adalimumab, golimumab and certolizumab pegol) tend to be mild and self-limiting.[21] Infusion reactions associated with intravenous TNF inhibitor administration (infliximab) may be acute (onset within 24 hours) or delayed (onset between one and 14 days later).[22]

Infusion reactions may be difficult to distinguish from viral infections or a drug-induced 'lupus-like' syndrome. Most acute infusion reactions are mild, and the patient presents with headache, flushing, dizziness, nausea or palpitations. Severe acute reactions occur less commonly, with the patient presenting with urticaria and anaphylaxis. Premedication with hydrocortisone, antihistamines or paracetamol can result in fewer acute infusion reactions.

Delayed infusion reactions are characterised by arthralgia, myalgia, fatigue and rash. They can be more difficult to treat than acute reactions and may require either corticosteroids or the withdrawal of anti-TNFα therapy. [22]

What are the precautions and contraindications?

TNF inhibitor therapies are generally safe and well tolerated. The most important safety concerns relate to an increased risk of infection and malignancy – the former being more likely in patients taking concomitant prednisolone at doses of 10 mg per day or more.[21] Careful consideration is required before prescribing TNF inhibitors in patients with comorbidities or underlying conditions that predispose them to infection.[23] TNF inhibitors are also contraindicated in patients with active (e.g. acute hepatitis B and C) or chronic infections, demyelinating disease or New York Heart Association class III or IV congestive heart failure.[14,21]

In patients previously exposed to tuberculosis there is a risk of reactivation. Routine screening for tuberculosis (chest x-ray, interferon gamma release assay) should therefore be undertaken before beginning treatment with TNF inhibitors.[21,24]

TNF inhibitors and infection

Reports derived from large registry databases found an increased risk of skin and soft tissue infections in patients with RA who were treated with TNF inhibitors compared with patients treated with traditional DMARDs.[25]

Serious infections are most likely to occur in the first six months of treatment with TNF inhibitors but can occur in subsequent years. No increased risk of serious adverse events were otherwise identified.[21] Patients should be cautioned about eating raw or undercooked eggs, meat or unpasteurised milk with the inherent risk of exposure to *Listeria*, *Salmonella* and other intracellular organisms.

There are also rare reports of John Cunningham virus reactivation with the use of TNF inhibitors and the development of progressive multifocal leucoencephalopathy.

TNF inhibitors and malignancy

To date, registry data do not generally support an increased incidence of malignancy with TNF inhibitor therapy. There is, however, a possible small increase in the risk of nonmelanoma skin cancers.[5] Annual skin checks are prudent for patients taking TNF inhibitors.

A possible increase in risk of lymphoma in patients with juvenile arthritis and adult RA treated with TNF inhibitors has been reported. The relative contribution of TNF inhibitor use to this risk is unclear, given RA disease activity and prior exposure to other DMARDs are both recognised risk factors for developing lymphoproliferative diseases.[26] Continued surveillance is needed before definitive conclusions can be drawn.

TNF inhibitors and vaccinations

Live vaccinations, including the varicella zoster virus, oral polio, measles mumps and rubella, and yellow fever vaccines, are contraindicated and must not be administered in patients receiving immunosuppressive therapy.[22]

Pap testing

Women being treated with TNF inhibitors may need to undergo more frequent gynaecological assessment, including Pap smears to exclude human papilloma virus infection or cervical dysplasia, than is usually recommended.[22]

Safety in pregnancy and breastfeeding

Women are generally advised to suspend TNF inhibitor therapy prior to conception and during pregnancy. Clinical uncertainty regarding the teratogenic risk of anti-TNF therapy remains.[21] From limited experience in patients with inflammatory bowel disease, no untoward or unexpected toxicity has been found with the deliberate or inadvertent use of TNF inhibitor therapy prior to conception or during pregnancy.[27] As infliximab is transported in utero late in pregnancy, treatment with this agent is not advised during the last trimester of pregnancy.[28]

Although TNF inhibitors are not excreted in breast milk, breastfeeding while taking these agents is not recommended.[14,29]

SUMMARY

Early diagnosis and treatment of patients with RA is the most effective strategy to induce disease remission, and therefore to prevent irreversible joint damage and long-term disability. In patients previously refractory to conventional DMARDs, the availability of TNF inhibitors represents a significant advance in treatment. The combination of TNF inhibitors and methotrexate shows significant improvements in clinical, radiographic and functional outcomes.

GPs should be aware that TNF inhibitors may diminish the normal signs of infection such as fever, particularly when corticosteroids are also being prescribed. Further research into the long-term safety and therapeutic profiles of these new biological DMARDs is needed as the therapeutic armamentarium of this class continues to expand. MT

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A list of references is available on request to the editorial office.

FURTHER READING

Updated recommendations for the use of biological agents for the treatment of rheumatic disease: Australian Rheumatology Association; 2011. Available online at: www.rheumatology.org.au/downloads/FINAL-BiologicalRecommendations060111.pdf (accessed September 2011).

This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

COMPETING INTERESTS: None.

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