Using Biologics Safely

Ernest H Choy.

CREATE Centre, Section of Rheumatology, Division of Infection and Immunity, Cardiff University, Cardiff, UK

Correspondence: Professor Ernest Choy, CREATE Centre, Section of Rheumatology, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff University, Cardiff, UK CF14 4XN. Email: choyeh@cardiff.ac.uk

This year marks the 20th anniversary of the first biologic Disease Modifying Anti-Rheumatic Drug (bDMARD), infliximab, a tumour necrosis factor inhibitor, approved for the treatment of rheumatoid arthritis (RA). It heralds two decades of "targeted" treatments for inflammatory arthritis with seven classes of biologic DMARDs (bDMARDs) plus target synthetic DMARDs (tsDMARDs): the janus kinase inhibitors. They have transformed the outcome of inflammatory arthritis with millions of patients having been treated globally. Their therapeutic benefit is indisputable. However, bDMARDs are potent immunosuppressive agents associated with significant risk of potentially serious side effects. Clinical vigilance is necessary to maximize benefit and mitigate against the risk of serious complications. To this end, the British Society for Rheumatology and British Healthcare Professional for Rheumatology have produced new guidelines on bDMARD safety in inflammatory arthritis[1] based on a large systematic review. It supersedes previous guidelines on tumour necrosis factor (TNF) inhibitors[2], rituximab[3] and tocilizumab[4] for RA. The new guidelines included patients with psoriatic arthritis (PsA) and axial spondyloarthritis (SpA) as well as the bDMARDs: abatacept and ustekinumab. However, they only apply to adult patients and exclude biologics approved by NICE after June 2016 (secukinumab and sarilumab), tsDMARDs and biosimilars. It also does not cover safety in the context of pregnancy and breastfeeding, which has been addressed by separate guidelines[5].

There are several important differences between the new and previous guidelines. Regarding infection, the new guideline recommended using etanercept or abatacept as a first line biological therapy in patients at high risk of infection and stated that the risk of tuberculosis (TB) reactivation is higher with anti-TNF monoclonal antibodies (notably adalimumab and infliximab) than for etanercept. If patients require anti-TNF therapy and have a high risk of TB reactivation, etanercept is preferred. Furthermore, these high-risk patients should be reviewed every 3 months. The guidelines on assessing and management of these patients are in part based on the "2005 British Thoracic Society recommendations on assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment" [6]. The definition of "high risk" was based on the incidence of tuberculosis in England and Wales. Given the data were more than 10 years old, an update would have been helpful. The guideline committee considered that relatively few large long-term studies have examined the risk of TB reactivation in non-TNF inhibitor biologics, so cautiously advised Rheumatologists to follow the TB screening practice as for anti-TNF agents but noted that the incidence of TB reactivation for abatacept, rituximab and tocilizumab, is low. Reactivation of varicella zoster (shingles) is a risk associated with janus kinase inhibitors although it has been reported also in patients treated by biologic agents. In patients without a past history of chickenpox, confirmed by a negative varicella zoster virus antibody test, the new guideline recommend varicella zoster vaccination should be offered prior to biologic treatment unless there are contraindications such as concurrent high dose prednisolone, methotrexate or azathioprine. However, if the patient did not receive zoster vaccination and has been exposed to primary varicella infection, prophylaxis with varicella zoster immune globulin should be considered if the risks from infection are perceived to be significant.

Regarding malignancy, the committee reckoned that there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease linked with biologic therapy. However, there is a potential association between non-melanotic skin cancers with anti-TNF

therapy, hence advice on the need for preventative skin care, skin surveillance and prompt reporting of new persistent skin lesions. In patients who have had prior treatment with >150 PUVA and/or >350 UVB phototherapy, the new guideline recommended discussion with a dermatologist prior to commencing anti-TNF therapy. This information may not be readily available to the Rheumatology team. However, in the biologic era, patients are less likely to be treated with high dose phototherapy.

Managing RA patients with interstitial lung disease (ILD) is challenging, the available evidence is limited and conflicting. The new guideline emphasized that interstitial lung disease is not an absolute contraindication to biological therapy. However, in patients with poor respiratory reserve, consulting a respiratory physician with a specialist interest in ILD would be advisable. All patients with ILD receiving biologic therapy should be jointly managed with a respiratory physician and have regular monitoring of pulmonary function. The new guideline recommended stopping biological therapy in patients with worsening or new features of ILD. The committee recommended rituximab or abatacept may be considered first-line biologic in patients with ILD.

Since the publication of previous guidelines, adalimumab has been approved by the Food and Drug Administration and European Medicine Agency for the treatment of non-infectious uveitis. In the new guideline, adalimumab and infliximab have been recommended as preferred anti-TNF therapy in patients with uveitis. However, uveitis has been reported following anti-TNF therapy especially after etanercept treatment[7].

For patients scheduled for surgery, the guideline highlighted that there is a balance between the risk of perioperative disease flare versus the risk of infection and wound healing. The latter is dependent on the surgical procedure. For low-risk procedures, a gap of one dosing interval is recommended. For higher risk procedures, stopping biologic agent 3-5 half-lives before surgery is recommended. One assumes that this will also apply to patients at high risk of infection. For patients receiving rituximab, the recommended interval is 3-6 months prior to surgery. Whilst for patients receiving tocilizumab, the interval should be 4 weeks for intravenous treatment and two weeks for subcutaneous therapy.

The guideline committee should be congratulated on these recommendations based on a comprehensive review of the evidence. Furthermore, these guidelines differ from other systematic reviews such as published by EULAR[8] in that practical recommendations on choice of biologic is given such as rituximab and abatacept in patients with ILD. The challenge for the committee is to update these guidelines to include new treatments in a timely fashion. Perhaps the committee can also consider making recommendations on practical clinical issues such as: should the same screening be performed in biologics naïve patients versus patients switching biologic treatment. Furthermore, registries have found that patients with multiple comorbidities are at risk of side effects from biologic treatment. How can these at high risk be identified in clinical practice? Should monitoring and treatment be different in these high-risk patients?

[1] Holroyd R et al. BSR/ BHPR Biological DMARD safety guidelines in inflammatory arthritis. Rheumatology Oxford 2018.

[2] Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology (Oxford). 2010 Nov;49(11):2217-9.

[3] Bukhari M, Abernethy R, Deighton C, et al. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Rheumatology (Oxford). 2011 Dec;50(12):2311-3.

[4] Malaviya AP, Ledingham J, Bloxham J, et al. The 2013 BSR and BHPR guideline for the use of intravenous tocilizumab in the treatment of adult patients with rheumatoid arthritis. Rheumatology (Oxford). 2014 Jul;53(7):1344-6.

[5] Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016 Sep;55(9):1693-7.

[6] British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax. 2005;60(10):800-5.

[7] Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumour necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis & Rheumatism. 2007;56(10):3248-52.

[8] Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014 Mar;73(3):529-35.