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**Using Biologics Safely**

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

19  
20 There are several important differences between the new and previous guidelines.  
21 Regarding infection, the new guideline recommended using etanercept or abatacept as a  
22 first line biological therapy in patients at high risk of infection and stated that the risk of  
23 tuberculosis (TB) reactivation is higher with anti-TNF monoclonal antibodies (notably  
24 adalimumab and infliximab) than for etanercept. If patients require anti-TNF therapy and  
25 have a high risk of TB reactivation, etanercept is preferred. Furthermore, these high-risk  
26 patients should be reviewed every 3 months. The guidelines on assessing and management  
27 of these patients are in part based on the “2005 British Thoracic Society recommendations  
28 on assessing risk and for managing Mycobacterium tuberculosis infection and disease in  
29 patients due to start anti-TNF- $\alpha$  treatment”<sup>6</sup>. The definition of “high risk” was based on the  
30 incidence of tuberculosis in England and Wales. Given the data were more than 10 years  
31 old, an update would have been helpful. The guideline committee considered that relatively  
32 few large long-term studies have examined the risk of TB reactivation in non-TNF inhibitor  
33 biologics, so cautiously advised Rheumatologists to follow the TB screening practice as for  
34 anti-TNF agents but noted that the incidence of TB reactivation for abatacept, rituximab and  
35 tocilizumab, is low. Reactivation of varicella zoster (shingles) is a risk associated with janus  
36 kinase inhibitors although it has been reported also in patients treated by biologic agents. In  
37 patients without a past history of chickenpox, confirmed by a negative varicella zoster virus  
38 antibody test, the new guideline recommend varicella zoster vaccination should be offered  
39 prior to biologic treatment unless there are contraindications such as concurrent high dose  
40 prednisolone, methotrexate or azathioprine. However, if the patient did not receive zoster  
41 vaccination and has been exposed to primary varicella infection, prophylaxis with varicella  
42 zoster immune globulin should be considered if the risks from infection are perceived to be  
43 significant.

44  
45 Regarding malignancy, the committee reckoned that there is no conclusive evidence for an  
46 increased risk of solid tumours or lymphoproliferative disease linked with biologic therapy.  
47 However, there is a potential association between non-melanotic skin cancers with anti-TNF

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

7  
8 Managing RA patients with interstitial lung disease (ILD) is challenging, the available  
9 evidence is limited and conflicting. The new guideline emphasized that interstitial lung  
10 disease is not an absolute contraindication to biological therapy. However, in patients with  
11 poor respiratory reserve, consulting a respiratory physician with a specialist interest in ILD  
12 would be advisable. All patients with ILD receiving biologic therapy should be jointly  
13 managed with a respiratory physician and have regular monitoring of pulmonary function.  
14 The new guideline recommended stopping biological therapy in patients with worsening or  
15 new features of ILD. The committee recommended rituximab or abatacept may be  
16 considered first-line biologic in patients with ILD.

17  
18 Since the publication of previous guidelines, adalimumab has been approved by the Food  
19 and Drug Administration and European Medicine Agency for the treatment of non-  
20 infectious uveitis. In the new guideline, adalimumab and infliximab have been  
21 recommended as preferred anti-TNF therapy in patients with uveitis. However, uveitis has  
22 been reported following anti-TNF therapy especially after etanercept treatment<sup>7</sup>.

23  
24 For patients scheduled for surgery, the guideline highlighted that there is a balance between  
25 the risk of perioperative disease flare versus the risk of infection and wound healing. The  
26 latter is dependent on the surgical procedure. For low-risk procedures, a gap of one dosing  
27 interval is recommended. For higher risk procedures, stopping biologic agent 3-5 half-lives  
28 before surgery is recommended. One assumes that this will also apply to patients at high  
29 risk of infection. For patients receiving rituximab, the recommended interval is 3-6 months  
30 prior to surgery. Whilst for patients receiving tocilizumab, the interval should be 4 weeks for  
31 intravenous treatment and two weeks for subcutaneous therapy.

32  
33 The guideline committee should be congratulated on these recommendations based on a  
34 comprehensive review of the evidence. Furthermore, these guidelines differ from other  
35 systematic reviews such as published by EULAR<sup>8</sup> in that practical recommendations on  
36 choice of biologic is given such as rituximab and abatacept in patients with ILD. The  
37 challenge for the committee is to update these guidelines to include new treatments in a  
38 timely fashion. Perhaps the committee can also consider making recommendations on  
39 practical clinical issues such as: should the same screening be performed in biologics naïve  
40 patients versus patients switching biologic treatment. Furthermore, registries have found  
41 that patients with multiple comorbidities are at risk of side effects from biologic treatment.  
42 How can these at high risk be identified in clinical practice? Should monitoring and  
43 treatment be different in these high-risk patients?

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- <sup>1</sup> Holroyd R et al. BSR/ BHPR Biological DMARD safety guidelines in inflammatory arthritis. Rheumatology Oxford 2018.
- <sup>2</sup> 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.
- <sup>3</sup> 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.
- <sup>4</sup> 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.
- <sup>5</sup> 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.
- <sup>6</sup> 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.
- <sup>7</sup> Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumour necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis & Rheumatism. 2007;56(10):3248-52.
- <sup>8</sup> 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.