Biological systemic treatment of psoriasis: reassurance on the risk of serious infection

A large UK prospective cohort study from the British Association of Dermatologists Biologic Interventions Register found that there was no statistically significant increase in the risk of serious infection with etanercept, adalimumab, or ustekinumab compared with non-biological systemic treatments or methotrexate-only. The MHRA highlighted that TNF-alpha inhibitors can increase susceptibility to infectious diseases, including tuberculosis (TB), and increase the risk of latent TB. While these agents are contraindicated in people with active TB or other severe infections, this new evidence provides some reassurance that the risk of future serious infection is not increased with biological treatments compared with non-biological treatments. The NICE guideline on psoriasis recommends tailoring the choice of systemic agent and the dosing schedule to the needs of the individual while considering: age; disease phenotype, pattern of activity and previous treatment history; disease severity and impact; presence of psoriatic arthritis (in consultation with a rheumatologist); conception plans; comorbidities and the person’s views. Ongoing monitoring for signs of infectious disease in line with MHRA advice is still an important consideration.

Overview and current advice

The NICE guideline on psoriasis recommends the choice of systemic therapy for people with psoriasis should be tailored to the needs of the individual, considering various factors including age, disease phenotype, disease severity, comorbidities and the person’s views. Methotrexate is usually the first-choice systemic agent, but ciclosporin and acitretin are preferred in certain circumstances. NICE has produced several technology appraisals on the biological agents that are currently licensed for the systemic treatment of psoriasis or psoriatic arthritis and further technology appraisals are underway. Biological agents are usually recommended when the psoriasis has not responded to standard systemic therapies including methotrexate, ciclosporin or PUVA (psoralen and ultraviolet-A light), or if the person is intolerant to them or has a contraindication to standard systemic therapies, as long as certain other criteria are met (see individual technology appraisals).

The NICE guideline on psoriasis highlights the importance of being aware of the benefits of, the contraindications to, and the adverse effects associated with systemic treatments. In particular biological agents have been associated with an increased risk of infection, including serious infections. In 2014 the MHRA highlighted that TNF-alpha inhibitors (such as adalimumab, certolizumab, etanercept, golimumab and infliximab) can increase susceptibility to infectious diseases, including tuberculosis (TB), and increase the risk of reactivation of latent TB. The MHRA advised that TNF-alpha inhibitors are contraindicated in people with active TB or other severe infections; patients should
be closely monitored for infectious diseases, including TB, before, during, and after treatment with a TNF-alpha inhibitor; they should be advised to seek medical advice if symptoms of TB develop during or after treatment and they should be given a patient alert card (produced by the manufacturer) that includes information on the risk of TB and other infectious diseases. This advice is reflected in the British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017 and the individual SPCs for all biological agents used in psoriasis.

The NICE guideline recommends that people with psoriasis who are starting treatment with a systemic non-biological or biological drug are offered the opportunity to participate in long-term safety registries, such as the British Association of Dermatologists Biologic Interventions Register. This is a large, ongoing, prospective pharmacovigilance registry of people with psoriasis that was established in 2007 in the UK and Ireland to compare the safety of biological therapies against non-biological systemic therapies (Yui et al. 2018).

The NICE interactive flowchart on psoriasis brings together all related NICE guidance and associated products on this topic in a set of interactive topic-based diagrams. See the Clinical Knowledge Summary information on psoriasis for a general overview of prescribing considerations.

**New evidence**

A prospective cohort study (n=9,038) assessed the risk of severe infection in people using biological agents for the management of psoriasis using data from the British Association of Dermatologists Biologic Interventions Register (Yui et al. 2018). Subjects were selected in a data snapshot from October 2016. People were included if they were naive to biological agents, but starting a biological therapy for chronic plaque psoriasis (n=5,617). The non-biological cohort (n=3,421) consisted of people with chronic plaque psoriasis, who were receiving either acitretin, PUVA, ciclosporin, fumaric acid esters, methotrexate or hydroxyurea. Only the biological agents etanercept (n=1,352), adalimumab (n=3,271) and ustekinumab (n=994) were included. There were not enough data on secukinumab and infliximab was excluded because the cohort using this drug had a higher disease severity and more comorbidities than people in the non-biological or other biological cohorts. Median follow-up time was 1.95 person-years (total follow-up time 13,370 person-years) for the biological agents and 1.51 person-years (total follow-up time 6,419 person-years) for the non-biological agents. A serious infection was defined as any infection that was associated with or prolonged hospitalisation, required the use of intravenous antimicrobial therapy, or led to death. Serious infection occurred in 283 people across both cohorts. For the different treatments, crude incidence rates per 1,000 patient years were: non-biological agents, 14.2 (95% confidence interval [CI] 11.5–17.4); methotrexate-only 12.0 (95% CI 8.82–16.27); etanercept 15.3 (95% CI 11.6–20.1); adalimumab 13.8 (95% CI 11.4–16.6); and ustekinumab 15.1 (95% CI 10.8–21.1).

When treatments were compared, and adjusted for confounding factors, no statistically significant increase in the risk of serious infection was found for etanercept (hazard ratio [HR] 1.10, 95% CI 0.75–1.60), adalimumab (HR 0.93, 95% CI 0.69–1.26), or ustekinumab (HR 0.92, 95% CI 0.60–1.41) compared with non-biological systemic treatments. The biological treatments were also compared with methotrexate-only as this is the most common non-biological systemic treatment used. However, there was still no statistically significant increase in the risk of serious infection found compared with methotrexate-only (etanercept: HR 1.47, 95% CI 0.95–2.28; adalimumab: HR 1.26, 95% CI 0.86–1.84; ustekinumab: HR 1.22, 95% CI 0.75–1.99).

The most common serious infections with biological and non-biological treatment were lower respiratory tract infections followed by skin and soft tissue infections and urinary tract infections. When organisms were identified, there were 13 staphylococcal, 10 streptococcal, 5 TB and 4 herpes zoster infections. No deaths within 30 days of the infection were seen with adalimumab and ustekinumab, less than 5 were seen with etanercept and 7 were seen with non-biological therapy. Use of
concomitant immunosuppressive treatment was not associated with an increase in the risk of serious infection.

A strength of this study is that it is the largest single registry cohort study assessing the risk of serious infection with first-line biological treatments for psoriasis and it included multiple dermatology centres based in the UK and Ireland. However, the authors acknowledge that the evidence is observational and, although it adjusted for confounding factors, some residual confounding may have remained (such as the inability to adjust for serious infection in the previous year).

**Commentary**

Commentary provided by Dr Antonia Lloyd-Lavery, Consultant Dermatologist, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust

Infections are the main adverse event leading to discontinuation of biological therapies in people with psoriasis, and serious infections are associated with significant morbidity and mortality. Risk of infection may therefore concern both clinicians and patients when making the decision to switch from using non-biological systemic agents to biological agents. It has been difficult to ascertain the real world infection risk using biological agents to treat psoriasis as clinical trials have limited external validity and are not powered to assess this outcome. Unsurprisingly, three prospective observational cohort studies using different methodologies and comparators have previously reported conflicting results (Dávila-Seijo et al. 2017, Garcia-Doval et al. 2017, Kalb et al. 2015).

Using the British Association of Dermatologists Biologic Interventions Register (BADBIR), a large, national, prospective psoriasis registry, the authors of this study (Yui et al. 2018) found no biological therapy was associated with a statistically significant increase in the risk of serious infection compared to non-biological systemic treatments. (Note, only adalimumab, etanercept and ustekinumab were included.) Neither was there a statistically significant increase in the risk of serious infection for each of the biological agents compared to methotrexate, the most commonly prescribed non-biological systemic treatment. Concomitant use of immunosuppressive treatments with biological therapies was also not associated with an increase in the risk of serious infection. No particular type of serious infection appeared to be associated with biological treatments.

The results of this well-designed study, which included a large sample size from 153 dermatology centres in the UK and Ireland, are reassuring, indicating that the risk of future serious infection is not significantly different between non-biological systemic therapies and the biological agents adalimumab, etanercept and ustekinumab. Importantly, the data highlight that vigilance in monitoring for infection is as important when using non-biological immunosuppressive therapies for psoriasis as it is for biological agents. Contrary to previous perception, etanercept may not have a lower infection risk based on its lower efficacy. These results reinforce the updated British Association of Dermatologists guideline for biologic therapies in psoriasis 2017 which recommend adalimumab and ustekinumab as first-line biological therapies (along with secukinumab). Of note, the more recently approved biological agents for psoriasis, secukinumab and ixekizumab, were not included in this study and the authors specifically excluded infliximab due to the limited power to study this particular agent using the BADBIR data. These results cannot be extrapolated to other conditions such as rheumatoid arthritis where biological agents inhibiting TNF-alpha have been associated with increased risk of serious infection.

The NICE guideline on psoriasis recommends tailoring the choice of systemic agent and the dosing schedule to the needs of the individual and considering age; disease phenotype, pattern of activity and previous treatment history; disease severity and impact; presence of psoriatic arthritis (in consultation with a rheumatologist), conception plans, comorbidities and the person's views. Ongoing monitoring for signs of infectious disease in line with MHRA advice is still an important consideration.
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References


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