



Medicines evidence commentary

commentary on important new evidence from medicines awareness weekly

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Interleukin inhibitors: risk of infections and cancer in people with rheumatologic diseases

A large systematic review and meta-analysis of randomised controlled trials in people with rheumatological diseases found that, compared with placebo, interleukin inhibitors increase the risk of serious infections (over a median of 24 weeks), opportunistic infections (54 weeks) and cancer (28 weeks). There are some limitations to the data. In particular, the time period to detect cancers was short and this needs to be confirmed further using some real-world data from long-term epidemiological studies. However, this study's attempt to quantify the risks may be a useful starting point for [shared decision making](#) when considering initiating an interleukin inhibitor for people with rheumatologic diseases.

Overview and current advice

The NICE guideline on [rheumatoid arthritis in adults](#) recommends trying biological and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs), if needed, after first trying the conventional DMARDs, methotrexate, leflunomide, sulfasalazine or hydroxychloroquine. More detailed recommendations on specific agents and how to use them are given in various NICE technology appraisals, many of which cover their use in other rheumatologic diseases such as psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis. Interleukin inhibitors, such as anakinra, baricitinib, ixekizumab, sarilumab, secukinumab, tocilizumab and ustekinumab fall under this category of medicines and are included in various pieces of NICE guidance on rheumatologic diseases. (Note, the NICE guideline specifically does not recommend using anakinra in rheumatoid arthritis, but for people who were already on anakinra, it advises that they should continue until they and their consultant consider it is appropriate to stop).

[The British Society for Rheumatology \(BSR\) biologic DMARD safety guidelines in inflammatory arthritis 2018](#) state that the decision to initiate a biological DMARD should be made in conjunction with the patient/carer and initiated by an expert in the management of rheumatic disease. The increased risk of infections with biological

DMARDs is well-known and the BSR guidelines recommend that biological DMARDs are used with caution in people who are at high risk of infection, after discussing the risks and benefits. Also, they should not be started in people who have an active serious infection. In addition, several baseline tests are recommended before starting treatment, including a full blood count and all patients should be screened for the presence of tuberculosis before starting treatment.

There have also been concerns over the risk of malignancy with biological DMARDs. Current advice from the BSR is that biological therapies should not be started in people with clinical signs of, or under investigation for, malignancy (basal cell carcinoma excluded). Caution should be exercised in the use of these medicines in people with previous malignancy and in people who have pre-malignant conditions (see the [BSR guidelines](#) for more detailed recommendations on managing these risks). These guidelines are specifically for people who have rheumatoid arthritis and not other conditions, or certain populations, such as people aged under 18 years. In addition, they do not cover biological DMARDs approved by NICE after June 2016 (such as the interleukin inhibitors secukinumab and sarilumab). However, there has been an overall lack of data available on the safety profile of the interleukin inhibitors ([Bilal J, 2019](#)). There are currently no specific recommendations issued by the MHRA on managing the risk of malignancy with biological DMARDs or interleukin inhibitors. The NICE Pathways on [arthritis](#) bring together everything NICE has said on managing these conditions.

New evidence

A [meta-analysis](#) of 74 [randomised controlled trials \(RCTs\)](#) in 29,214 people with rheumatologic diseases looked at the risks of serious infections, opportunistic infections and cancer with interleukin inhibitors compared with placebo ([Bilal J, 2019](#)). Almost half the studies (35) were in rheumatoid arthritis, 12 in psoriatic arthritis, 9 in ankylosing spondylitis and 5 or fewer were in gout, juvenile idiopathic arthritis, giant cell arteritis, systemic lupus erythematosus, primary Sjogren syndrome, systemic sclerosis, familial Mediterranean fever and osteoarthritis. The interleukin inhibitors used in the RCTs were tocilizumab (18 RCTs), secukinumab (15), anakinra (8), ixekizumab (6), rilonacept (6), sarilumab (4), sirukumab (4), ustekinumab (4), brodalumab (3), guselkumab (2), clazakizumab (2), canakinumab (1) and olokizumab (1). Note, rilonacept, clazakizumab and olokizumab are not currently licensed within the UK. Publication dates ranged from 2002 to 2018. A continuity correction (to reduce bias where events are infrequent) was applied to results if no events were observed in 1 of the study arms and a [sensitivity analysis](#) was also carried out that did not include this continuity correction.

For serious infections, 69 RCTs (n=24,236; 17,177 receiving interleukin inhibitors and 7,059 receiving placebo) had data available for analysis. The median duration of trials and/or safety follow-up was 24 weeks (range 4 to 156 weeks). A total of 486

serious infections were reported in people receiving interleukin inhibitors compared with 96 in those on placebo. The pooled [odds ratio](#) (OR) showed a [statistically significant](#), approximate doubling, of the risk of serious infections with interleukin inhibitors compared with placebo (OR, 1.97; 95 % [confidence interval](#) [CI], 1.58 to 2.44; $p < 0.001$). These results were judged to have 'high certainty' by [GRADE](#) criteria and they were similar after [sensitivity analysis](#) (adjusted OR, 1.93; 95% CI, 1.56 to 2.39; $p < 0.001$).

Opportunistic infections were reported in 14 RCTs (n=9,998; 7,153 receiving interleukin inhibitors and 2,845 placebo). The median duration of trials and/or safety follow-up was 54 weeks (range 24 to 264 weeks). A total of 43 opportunistic infections were reported in people receiving interleukin inhibitors compared with 5 in those on placebo. Over half of these (23) were oral candidiasis, 9 herpes zoster, 4 oesophageal candidiasis, 1 unspecified candidiasis, 2 tuberculosis, 2 atypical mycobacterial infections, and 6 unspecified. As was found with serious infections, a statistically significant increase in the risk of opportunistic infections was reported with interleukin inhibitors (OR, 2.35; 95% CI, 1.09 to 5.05; $p = 0.03$; moderate certainty). This was no longer statistically significant when compared with placebo after sensitivity analysis without a continuity correction (adjusted OR, 1.95; 95% CI, 0.99 to 3.82; $p = 0.05$).

Cancers were reported in 45 RCTs (n=21,065; 15,244 receiving interleukin inhibitors and 5,821 placebo). The median duration of trials and/or safety follow-up was 28 weeks (range 12 to 264 weeks). A total of 141 cases of cancer were reported in the interleukin inhibitor group compared with 28 with placebo. There was also a statistically significant increased risk of cancer with interleukin inhibitors (OR, 1.52; 95% CI, 1.05 to 2.19; $p = 0.03$; moderate certainty), with similar results after sensitivity analysis (adjusted OR, 1.47; 95% CI, 1.04 to 2.08; $p = 0.03$).

Commentary

Commentary provided by NICE

This large [study](#) suggests that, as with other biological DMARDs, interleukin inhibitors are associated with an increased risk of serious infections, opportunistic infections and cancer compared with placebo, when given to people with rheumatologic diseases. The authors estimated that this equates to a [number needed to harm](#) (NNH) of 67 for 1 additional serious infection within a median follow-up of 24 weeks, 250 for opportunistic infections (median follow-up, 54 weeks) and 250 for cancer (median follow-up, 28 weeks). With almost 30,000 participants in the RCTs included, this systematic review adds considerably to the limited evidence on the safety profile of interleukin inhibitors and, by using the robust [GRADE](#) criteria to consider the quality of the studies, the effect on serious infections was considered of high certainty and for opportunistic infections and cancer it was of moderate certainty.

As highlighted by the authors, it is important to note that there are some limitations to these findings. It was not able to compare the effects of different interleukin inhibitors or dosages and it only considers the effect of these medicines as a group. In addition, study participants may have been taking other immunosuppressive medicines too (such as prednisolone), which might have affected the risks reported. Also, it assumes that the risks of infection and cancer are constant over time, even though this has not necessarily been the case with other biological DMARDs. Furthermore, a median follow-up of 28 weeks is too short to assess the full risk on cancers that may take many years to develop. This needs to be confirmed further using some real-world data from long-term epidemiological studies. Note, these results apply only to the use of interleukin inhibitors in people with rheumatologic diseases, a large proportion of whom had rheumatoid arthritis.

The benefits of biological DMARDs for some people with rheumatologic disease can be significant and life changing. However, and despite some limitations, this study quantifies the risks of infections and cancer to provide useful information to inform [shared decision making](#) conversations in those considering initiating an interleukin inhibitor. NICE has produced a variety of resources on shared decision making. This includes [patient decision aids](#) for a variety of decisions in different conditions and the NICE [key therapeutic topic on shared decision making](#). The NICE Pathway on [medicines optimisation](#) brings together everything NICE has said on this topic. NICE is also developing a [guideline on shared decision making](#). It is expected to be published in April 2021 and will give formal NICE guidance on implementing shared decision making.

Study sponsorship

None noted for this systematic review.

References

Bilal J, Berlinberg A, Riaz B et al. (2019) [Risk of Infections and Cancer in Patients With Rheumatologic Diseases Receiving Interleukin Inhibitors: A Systematic Review and Meta-analysis](#) JAMA Netw Open;2:e1913102.

About this medicines evidence commentary

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