Proposal for sequential interleukin (IL) inhibitor use

Consider managing IL inhibitor sub-types as drugs with a different mechanism of action, allowing for a switch between the IL inhibitor sub-types as follows:

- IL-17, IL-23 and IL-12/23 inhibitors for psoriasis
- IL-17, IL-23 and IL-12/23 inhibitors for psoriatic arthritis
- IL-23 and IL12/23 inhibitors for Crohn's disease

This would not include switching between the same sub-type of IL inhibitor (e.g. between Ixekizumab (IL-17) and Secukinumab (IL-17)).

Rationale Summary

- Currently sequential use of IL inhibitors is not commissioned by SWL, because SWL had not yet considered the available evidence.
- There are now more sub-types of IL inhibitors available (see appendix 1), which are commissioned in line with NICE TA criteria and SWL agreed pathways.
- It is recognised that different IL inhibitors may target the same pathway but have a varying mechanism of action.
- No evidence is available to understand the cost-effectiveness of using sequential IL inhibitors. The "law of diminishing returns" suggests the more advanced therapies a patient receives, the lesser the overall benefit to the patient.
- There is a cohort of patients who have contra-indications to TNF-alpha inhibitors and to JAK inhibitors. This limits their treatment options.
- Where there is a NICE TA for more than one type of IL inhibitor for a given condition (i.e., atopic dermatitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease), consideration should be given to treat these IL inhibitors as separate drug classes.
- RMOC advice on "Sequential use of biologic medicines" (May 2020) states that:
  - Prescribing choices should be made on grounds of clinical and cost-effectiveness and ensuring that the most appropriate and safe treatment option is selected through shared decision-making.
  - The NHS Constitution pledges that patients have the right to drugs and treatments that have been recommended by NICE subject to being clinically appropriate, and patients have the right to expect local decisions on the funding of drugs and treatments to be made rationally and following the proper consideration of evidence.
  - Clinical assessment of the appropriateness of treatments should be the overriding factor rather than the implementation of policies for costs saving reasons.
  - Guidance from specialist bodies suggest switching to a biologic with a new mechanism of action is more effective than switching within class (based on low quality evidence; anti-TNF treatment is an exception).
- Recently published NICE TA guidance (TA888), infer that IL17, IL23 and IL12/23 inhibitor are different drug classes.
- There are 2 NICE TA approved IL inhibitors for atopic dermatitis, i.e. dupilumab (IL4/13 inhibitor) and tralokinumab (IL13 inhibitor). However, it is currently unclear if they should be considered as 2 distinct drugs classes and there is no information in the NICE TAs to guide us. This will be reviewed when updating the atopic dermatitis pathway (along with the psoriasis pathway) with dermatology colleagues.

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Background

Advanced therapies are used when conventional therapies fail to provide adequate therapeutic response, or are contra-indicated for use, providing patients meet criteria stipulated by NICE.

Examples of advanced therapies commissioned in SWL include TNF-alpha inhibitors, JAK inhibitors and interleukin (IL) inhibitors.

The SWL COVID-19 interim policy and process for considering Locally Commissioned PbR-excluded drug requests in line with RMOC advisory statement on:

"sequential use of biologic medicines" indicates that sequential use of IL inhibitors is not permitted:

"*Interleukin inhibitors (no differentiation between IL inhibitors will be applied at this stage as we have not had the opportunity to consider the evidence for sequential IL inhibitor use– applications for an alternative IL will need to come via IFR with the clinician providing the evidence).*"

Recently published NICE TAs infer the IL17, IL23 and IL12/23 inhibitor sub-types to be of separate drug classes. NICE TA888 (Risankizumab for Crohn's disease) indicates Risankizumab (IL-23) as an IL inhibitor is a "*novel treatment with a different mechanism of action to existing treatments*", despite approval for Ustekinumab (IL-12/23) having been granted several years earlier. NICE TA907 on Deucravacitinib for treating moderate to severe plaque psoriasis indicates the same.

This topic of sequential use of IL inhibitors has been discussed with a pharmacologist at St Georges Hospital, Dr Andrew Hitchings, who outlined that IL inhibitors are too different to be treated as a single class, but equally cost-effectiveness of sequential use of IL inhibitors is not always a consideration in NICE TAs.

NICE's position on the sequential use of IL inhibitors is summarised neatly in NICE TA511 (Brodalumab for treating moderate to severe plaque psoriasis), which recognises that an IL inhibitor "*may target the same pathway as, but has a different mechanism of action from, other interleukin-17 inhibitors; it targets a different part of the pathway*". But concluded that "*without evidence on the benefit of targeting a specific part of the pathway, there were no additional gains in health-related quality of life over those already included in the QALY calculations*".

NICE TAs typically compare cost-effectiveness of IL inhibitors against other IL inhibitors, rather than in a treatment sequence. The exception is for some psoriasis IL NICE TAs where consideration was given to the use of one IL inhibitor after another. However, it noted that disease response to subsequent advanced therapy may be lower than the level of response achieved by the initial advanced therapy, or if that treatment had been used earlier in the treatment sequence ('law of diminishing return'). There is currently no evidence to show the extent to which effectiveness of treatments changes when used at different stages in therapy.

The current guidance that recommends switching to a biologic with a new mechanism of action being more effective than switching within class is based on low quality evidence; anti-TNF treatment is an exception.

Contra-indications to TNF-alpha inhibitors include progressing age, cardiovascular risk factors, and susceptibility to infections. A MHRA drug safety alert published 26 April 2023 for JAK inhibitors advised new measures to be introduced for patients aged over 65 years, or with cardiovascular risk factors or malignancy risk factors. This limits access to treatment options for those who have a contra-indication for TNF-alpha inhibitors or JAK-inhibitors.

Therefore, there is a cohort of patients who do not have many viable treatment options once they exhaust one IL inhibitor or who have exhausted all other treatment options.

We have noted that neighbouring organisations with pathways (Surrey, South East London and North East London) are treating the different IL-inhibitors as different drug classes.

References:

1. COVID-19 interim policy and process for considering Locally Commissioned PbR-excluded drug requests in line with RMOC advisory statement on “sequential use of biologic medicines”
2. NICE TA456: Ustekinumab for moderately to severely active Crohn’s disease after previous treatment. 12 July 2017
3. NICE TA888: Risankizumab for previously treated moderately to severely active Crohn’s disease. 17 May 2023
4. NICE TA511: Brodalumab for treating moderate to severe plaque psoriasis. 21 March 2018

Appendix 1: Overview of available IL inhibitors and NICE approved indications

Indication	Drug	IL sub-type
Rheumatoid arthritis	Sarilumab	IL-6
	Tocilizumab	
Atopic dermatitis	Dupilumab	IL-4 + IL-13
	Tralokinumab	IL-13
Psoriasis	Bimekizumab	IL-17
	Brodalumab	IL-17
	Ixekizumab	IL-17
	Secukinumab	
	Guselkumab	IL-23
	Risankizumab	
	Tildrakizumab	
	Ustekinumab	IL-12 + IL-23
Ankylosing spondylitis	Ixekizumab	IL-17
	Secukinumab	
Nr-axial spondyloarthritis	Ixekizumab	IL-17
	Secukinumab	
Psoriatic arthritis	Ixekizumab	IL17
	Secukinumab	
	Guselkumab	IL-23
	Risankizumab	
	Ustekinumab	IL-12 + IL-23
Crohn's disease	Risankizumab	IL-23
	Ustekinumab	IL-12 + IL-23
Ulcerative colitis	Ustekinumab	IL-12 + IL-23

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