EXPERT RECOMMENDATIONS ON THE USE OF B/TSDMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO FIRST-LINE TNFi

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Background:

- There is growing interest in personalised and holistic attention to patients with rheumatoid arthritis (RA).
- Tumour necrosis factor inhibitors (TNFi) are usually the first-line biological therapy.
- However, ~ 40% of RA patients will experience an inadequate response to TNFi, and there is no clear guide on how to select the subsequent therapy.

Objective:

- To establish practical recommendations for the management of patients with RA and an inadequate response to first-line TNFi with a special focus on a personalised approach.

Methods:

- A **steering committee** composed of 5 rheumatologists with expertise in RA was established.
- **Subgroups of RA patients with a first-line inadequate response to TNFi** were identified based on specific characteristics/treatment strategies that might influence the selection of subsequent biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).
- A **large scoping review** (LSR) was performed to analyse the efficacy and safety of b/tsDMARDs in these patient subgroups / treatment strategies.
- In a nominal group meeting, the steering committee discussed the results of the LSR and proposed a set of **recommendations**.
- Recommendations were tested in a **Delphi process** in which another group of 30 expert rheumatologists were invited to participate. Agreement was defined if ≥70% of the participants voted ≥7 (from 1, totally disagree to 10, totally agree).
- A **decision tree for treatment selection** for each patient subgroup / treatment strategy was created based on the LSR, indirect evidence (data from other RA populations, drug mechanism of action, physiopathological findings, etc.) and on the experts' opinions.

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Results:

- The LSR included 43 articles, all exploratory analyses of randomized controlled trials. The results revealed a high heterogeneity regarding populations, type and use of b/tsDMARDs or outcomes.
- N=17 recommendations were generated.
- All but 2 recommendations reached the predefined agreement level in the Delphi process (Table 1). Figure 1 shows the decision tree for treatment selection.

Table 1. Main results of the Delphi process.

#	Recommendation	Mean	SD	%≥7*	LE†	GR†
1	In RA patients aged >65 years, JAKis should be used with caution and only if no suitable treatment alternatives are available	8.33	1.32	86.4%	3a	B
2	In patients with RA and inadequate response to ≥2 TNFis, a switch to a drug with a different mechanism of action is recommended	7.67	2.38	73.3%	3b	B
3	In RA patients requiring biological therapy as monotherapy, an IL6i or JAKi is recommended as the preferred choice	8.87	1.14	96.7%	2b	B
4	bDMARDs and tsDMARDS can be prescribed irrespectively of baseline rheumatoid factor and anti-citrullinated peptide antibody status	7.77	2.27	77.4%	3b	C
5	In RA patients with an important systemic inflammatory component, the use of an IL6Ri is recommended	8.63	0.96	96.7%	3a	B
6	In RA patients with interstitial lung disease, RTX, ABT, IL6Ris, or JAKis are recommended as the preferred choice	8.30	1.99	93.3%	4	C
7	In patients with rheumatoid vasculitis, it is recommended to use RTX, preferably	8.63	1.77	86.4%	4	C
8	In RA patients with high cardiovascular risk or a previous cardiovascular event, JAKis should be avoided	9.30	1.06	96.7%	3a	B
9	In RA patients with risk factors for venous thromboembolic disease, JAKis should be avoided	9.20	1.00	100%	3a	B
10	Obesity in RA patients favours the use of medications other than TNFis	6.43	2.18	56.7%	-	-
11	For RA patients with a high risk of infection or a previous serious infection, ABT is preferably recommended. If an alternative treatment is considered, ETN may have advantages over other bDRMARDs or tsDRMARDs	8.23	1.79	93.3%	3b	C
12	bDMARDs and tsDMARDs can be used in patients with RA and osteoporosis, but tofacitinib should be used with caution in patients with known risk factors for fractures, such as elderly patients, female patients, and patients with corticosteroid use	6.17	2.31	43.3%	-	-
13	In RA patients with evidence of nociplastic pain, depression, fatigue, treatment with IL6Ris or JAKis can be considered	7.33	2.11	70%	3b	C
14	In RA patients with previous solid cancer, JAKis are not recommended	7.90	2.26	77.4%	3a	B
15	In RA patients with haematological cancer, RTX is preferably recommended	9.13	1.04	96.7%	2b	B
16	In RA patients with non-melanoma skin cancer, TNFis, ABT, and JAKis are not recommended	8.23	1.63	90%	3a	B
17	In pregnant women with RA and inadequate response to certolizumab pegol, a different TNFis can be safely prescribed	7.37	2.48	76.7%	3a	B

*Agreement was reached if at least 70% of participants voted ≥7. The participants voted each statement on a scale from 1 to 10 (1=totally disagree to 10=totally agree).
† The level of evidence (LE) and grade of recommendation (GR) were assessed using the Centre for Evidence-Based Medicine of Oxford [14].
Abbreviations: RA=rheumatoid arthritis; JAKi=janus kinase inhibitors; TNFi=tumour necrosis factor inhibitor; bDMARD=biologic disease-modifying anti-rheumatic drug; tsDMARD=targeted synthetic disease-modifying anti-rheumatic drug; IL6Ri=interleukin-6 receptor inhibitor; RTX=rituximab; ABT=abatacept; ETN=etanercept; SD=standard deviation.

Figure 1. Decision tree for treatment selection following first-line TNFi therapy in RA.

Target population / treatment strategy	2nd TNFi	RTX	ABT	IL6Ri	JAKi
>65 years					
Refractory to ≥2 TNFi					
Monotherapy	ETN				
RF and/or ACPA status					
Important systemic inflammatory component					
Interstitial lung disease					
Rheumatoid vasculitis					
High CV risk or a previous CV event					
Risk factors for venous thromboembolic disease					
High risk of infection or previous serious infection	ETN				
Nociplastic pain					
Depression, fatigue					
Previous solid cancer					
Haematological cancer					
Non-melanoma skin cancer					
Pregnant women and inadequate response to CZP					

Abbreviations: TNFi=tumor necrosis factor inhibitors; IL6Ri=Interleukin 6 receptor inhibitors; JAKi=Janus kinase inhibitors; CV=cardiovascular; CZP=certolizumab pegol; ETN=etanercept; RA=rheumatoid arthritis; RTX=rituximab; ABT=abatacept.

Legend of colours:
Purple: "strongly recommended" - robust (e.g., randomized controlled trials) direct (target RA population / treatment strategy) evidence.
Dark blue: "*highly recommended*" – direct but not robust evidence (e.g. exploratory analysis) and/or indi (different RA populations) but relevant evidence (e.g. randomized controlled trials, high-quality observational studies including biologic registries), and/or very plausible mechanism of action.
Light blue: "*recommended*" – not sufficient evidence for dark blue.
Grey: "*neutral*" - lack of or scarce evidence, no clear relationship with mechanism of action, etc.
Light red: "use with caution" - direct or indirect evidence regarding alarm signs.
Dark red: "*not recommended*" – relevant, robust direct or indirect evidence against its use.

Conclusions:

- Tailoring treatment to patient characteristics is essential for optimal outcomes.
- Although treatment decision-making is multifactorial and robust evidence is scarce, the proposed recommendations and treatment decision tree gather and synthesize the most valid available information to advise personalized treatment choices in RA patients with inadequate response to TNFis.

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