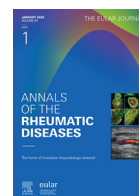




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## Recommendations

## EULAR recommendations for use of antirheumatic drugs in reproduction, pregnancy, and lactation: 2024 update

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Handling editor Josef Smolen.

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<https://doi.org/10.1016/j.ard.2025.02.023>

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Please cite this article as: L. Rüegg et al., EULAR recommendations for use of antirheumatic drugs in reproduction, pregnancy, and lactation: 2024 update, Ann Rheum Dis (2025), <https://doi.org/10.1016/j.ard.2025.02.023>

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## ARTICLE INFO

## ABSTRACT

**Objectives:** To update the existing European Alliance of Associations for Rheumatology (EULAR) points to consider (PtC) for use of antirheumatic drugs in reproduction, pregnancy, and lactation, including additional drugs and adverse outcomes as well as paternal drug safety.

**Methods:** According to the EULAR standardised operating procedures, an international task force (TF) defined the questions for a systematic literature review, followed by formulation of the updated statements. A predefined voting process was applied to each overarching principle and statement. Level of evidence and strength of recommendation were assigned, and participants finally provided their level of agreement for each item.

**Results:** The TF proposes 5 overarching principles and 12 recommendations for the use of anti-rheumatic drugs before and during pregnancy, through lactation, and in male patients. The current evidence indicates that synthetic disease-modifying antirheumatic drugs (DMARDs) compatible with pregnancy include antimalarials, azathioprine, colchicine, cyclosporine, sulfasalazine, and tacrolimus. Regarding nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, a more restrictive approach to their use during pregnancy is recommended. Based on an individualised risk-benefit assessment, all tumour necrosis factor inhibitor (TNFi) biologic DMARDs (bDMARDs) can be used throughout pregnancy, and non-TNFi bDMARDs may be used if needed. In relation to lactation, compatible drugs include antimalarials, azathioprine, colchicine, cyclosporine, glucocorticoids, intravenous immunoglobulin (IVIG), NSAIDs, sulfasalazine, and tacrolimus. All bDMARDs are considered compatible with breastfeeding. Concerning the use of drugs in men, compatible options include antimalarials, azathioprine, colchicine, cyclosporine, IVIG, leflunomide, methotrexate, mycophenolate, NSAIDs, glucocorticoids, sildenafil, sulfasalazine, tacrolimus, and bDMARDs.

**Conclusions:** The updated recommendations provide consensus guidance and will help to improve the quality of care of patients during the phases of reproduction, pregnancy, and lactation.

## INTRODUCTION

The management of patients with rheumatic and musculoskeletal disease (RMD) in the phase of reproduction, pregnancy and breastfeeding is a challenging task. Since 2016, guidance from the European Alliance of Associations for Rheumatology (EULAR) points to consider (PtC) for the use of antirheumatic drugs before pregnancy, and during pregnancy and lactation have been widely used [1]. Meanwhile, modern treatment approaches have evolved towards a treat-to-target concept to avoid the negative impact of active disease on fertility and pregnancy outcomes [2]. Additionally, new relevant data about antirheumatic drugs in the context of pregnancy and breastfeeding as well as in male reproductive health have emerged. Given these important advances, an update of the 2016 version was

needed. Given the body of new evidence, PtC were changed into recommendations. These recommendations on safety of antirheumatic drugs in female and male patients planning a family and in pregnant and breastfeeding women are intended to provide evidence-based guidance to clinicians, health professionals, patients, pharmaceutical companies, and regulatory organisations.

## METHODS

After approval by the EULAR Quality of Care committee, the convenor (FF) and methodologists (YM and AF) convened a task force (TF) according to the EULAR standardised operating procedures for developing PtC/recommendations. The 27 TF members comprised a multidisciplinary team of 13 rheumatologists

(including 3 fellows LR, AP, SH), 1 internal medicine doctor, 1 gastroenterologist, 1 obstetric physician, 1 obstetrician, 2 teratology specialists (1 from Embryotox and 1 from the Organization of Teratology Information Specialists [OTIS]), 1 pharmacist (LactMed), 2 methodologists, 1 healthcare professional, 2 Emerging EULAR Network (EMEUNET) representatives, and 2 patient representatives from a total of 13 countries. Prior to the project start, all TF members disclosed their conflicts of interest.

During the first virtual meeting in June 2022, research questions were defined by the TF as a basis for the systematic literature review (SLR). Going beyond the search criteria of the 2016 EULAR PtC [1], it was agreed that the SLR should include additional pregnancy outcomes, new drugs, and the safety of drugs in male patients planning to father a child. The SLR was carried out by the fellows under the supervision of the methodologists and the convenor. Methods and results of the SLR and of related meta-analyses are published separately [3,4,113]; however, the SLR and the present manuscript on recommendations form an integral and should be read as such.

The results of the SLR were presented at the face-to-face consensus meeting to all TF members in October 2023 and served as a basis for the formulation of overarching principles and recommendations. During the meeting, consensus about every overarching principle and recommendation was reached if >75% of members voted in favour of a statement. Following the approval of the statements, every member indicated their level of agreement (LoA) to each item on a 0 to 10 numeric rating scale (0 = ‘completely disagree’ to 10 = ‘completely agree’) anonymously via Survey Monkey. Means and standard deviations of the LoA and the percentage of members with LoA  $\geq 8$  were calculated. For each drug, the level of evidence (LoE) and grade of recommendation (GoR) was assigned according to the Oxford Centre for Evidence-Based Medicine (Supplementary Table S1) [5,6], and the LoE of the 2016 EULAR PtC was also considered [1].

Furthermore, a research agenda was set up based on gaps in evidence. The final manuscript was approved by all TF members and by the EULAR Executive Committee.

## RESULTS

The TF formulated a final number of 5 overarching principles and 12 recommendations (Tables 1–4). The detailed results of the SLR are published separately and as EULAR abstracts [3,4]; however, parts of the data are also included herein, to provide a rationale for the proposed recommendations.

### Overarching principles

The overarching principles reflect good clinical practice and the key aspects for counselling patients with RMD planning a family. These principles were consensus-based and did not result directly from the SLR. Compared to 2016, statement D was added, and other statements were revised.

**(A) All patients, females and males, should be offered early and regular counselling about reproductive health and the need for adjustment of therapy in relation to pregnancy.**

To avoid the risks of unplanned pregnancies in a phase of active disease or exposure to teratogenic drugs, the healthcare provider should offer counselling early and regularly to all patients of fertile age [7]. Counselling can be guided by the patient’s questions and concerns and must emphasise the importance of planned pregnancies and the use of compatible

medication. The discussed information should be shared with the multidisciplinary team involved in the care of the patient.

**(B) Treatment of patients with RMD before conception and during and after pregnancy should aim at remission or low disease activity.**

This principle highlights the importance of stable quiescent disease while on compatible medication as a prerequisite for improved outcome in both mother and child. This also applies to male patients planning to conceive. In case of active disease, conception should be postponed, and treatment be adjusted until optimal disease control is reached.

**(C) The potential risk of drug therapy for the foetus or child should be weighed against the risk of untreated maternal disease.**

Untreated maternal RMD is associated with a relevant increased risk of adverse pregnancy outcomes [8]. This important aspect needs to be taken into consideration for the risk-benefit analysis of an effective drug therapy in pregnancy. Evidence-based recommendations on pregnancy-compatible medication should be used to provide balanced information.

**(D) Given the benefits of breastfeeding, women should not be discouraged from breastfeeding while taking compatible medications.**

This new principle underlines the benefits of breastfeeding. For the infant, human milk provides the best option for improved outcomes, with short-term protection against infectious morbidity and mortality and long-term protection against inflammatory bowel disease, obesity, diabetes, and some childhood cancers [9]. For the mother, breastfeeding reduces the risks of diabetes; hypertension; and breast, ovarian, endometrial and thyroid cancer [9]. International medical societies recommend exclusive breastfeeding for approximately 6 months after birth [9,10]. Women should be informed about the beneficial effect of breastfeeding while taking compatible medication, and drugs with limited data should be discussed with patients.

**(E) The choice of treatment before, during, and after pregnancy should be a shared decision-making process between the treating healthcare providers and the patient.**

This principle highlights the importance of shared decision making regarding treatment choices in men and women before conception and in pregnant and breastfeeding women. The aim of the comprehensive counselling process should enable the patient to make an informed decision and reduce potential concerns [7].

### Recommendations

#### I. Antirheumatic drugs before and during pregnancy

**1. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and other drugs used in rheumatology practice that are compatible with pregnancy include hydroxychloroquine, chloroquine, azathioprine or mercaptopurine, cyclosporine, tacrolimus, sulfasalazine, and colchicine.**

The statement is unchanged from the previous version and contains proven pregnancy-compatible csDMARDs and other drugs used in rheumatology practice that should be continued for maintenance of remission or treatment of disease flares [1]. For these drugs, current evidence does not indicate an increased rate of congenital malformations or other adverse pregnancy outcomes [1,11–17].

With regard to the antimalarials, evidence for safety in pregnancy is mostly based on hydroxychloroquine at daily doses

**Table 1**  
**EULAR recommendations for use of antirheumatic drugs in reproduction, pregnancy, and lactation—2024 update**

		Level of agreement	
		Mean (SD)	% with scores $\geq 8$
<b>Overarching principles</b>			
(A) All patients, females and males, should be offered early and regular counselling about reproductive health and the need for adjustment of therapy in relation to pregnancy.		10 (0)	100
(B) Treatment of patients with rheumatic and musculoskeletal diseases before conception and during and after pregnancy should aim at remission or low disease activity.		9.88 (0.42)	100
(C) The potential risk of drug therapy for the foetus or child should be weighed against the risk of untreated maternal disease.		9.92 (0.26)	100
(D) Given the benefits of breastfeeding, women should not be discouraged from breastfeeding while taking compatible medications.		9.85 (0.53)	100
(E) The choice of treatment before, during, and after pregnancy should be a shared decision-making process between the treating healthcare providers and the patient.		9.92 (0.26)	100
<b>Recommendations</b>			
<b>I. Antirheumatic drugs before and during pregnancy</b>		Drug (listed alphabetically) with LoE/GoR of recommendation	
1. csDMARDs and other drugs used in rheumatology practice that are compatible with pregnancy include azathioprine or mercaptopurine, chloroquine, colchicine, cyclosporine, hydroxychloroquine, sulfasalazine, and tacrolimus.	2a/B azathioprine, 6-mercaptopurine	9.91 (0.40)	100
	2c/B chloroquine		
	2b/B colchicine		
	2a/B cyclosporine		
	2a/B hydroxychloroquine		
2. Cyclophosphamide, methotrexate, and mycophenolate are teratogenic and should be discontinued before pregnancy.	2a/B sulfasalazine	10 (0)	100
	2b/B tacrolimus		
3. NSAIDs, prednisone, and prednisolone can be considered during pregnancy if needed to control disease activity. Adding or switching pregnancy-compatible csDMARDs or bDMARDs should be considered if needed to control active disease.	2a/B cyclophosphamide	9.50 (1.60)	96.16
	2a/B nonselective NSAIDs (eg, ibuprofen, diclofenac)		
3a. In pregnancy, NSAIDs should only be used intermittently and stopped after 28 wk of gestation. Due to limited evidence on selective COX-2 inhibitors, nonselective NSAIDs with a short half-life (eg, ibuprofen) are preferred. Discontinuation of NSAIDs should be considered if there is difficulty in conceiving.	2b/C COX-2 inhibitors	9.73 (0.66)	100
	2a/B prednisone, prednisolone		
3b. In pregnancy, prednisone and prednisolone should be tapered where possible to a maintenance dose of $\leq 5$ mg/d and, when possible, withdrawn. The use of higher dosages should be weighed against the risk of maternal-foetal complications.		9.84 (0.46)	100
4. In severe, refractory maternal disease during pregnancy, IV methylprednisolone pulses, IVIG, sildenafil, pregnancy-compatible csDMARDs and/or bDMARDs, or, in the second and third trimesters, cyclophosphamide, or mycophenolate can be considered.	2a/B-5/D bDMARDs (see point 5)	9.40 (1.19)	96.00
	2a/B-2c/B csDMARDs (see point 1)		
	4/C cyclophosphamide in second/third trimester		
	3b/C IVIG		
	4/C IV methylprednisolone pulses		
5. For bDMARD use in pregnancy, individual drug effectiveness and transplacental transfer should be taken into consideration.	4/D mycophenolate in second/third trimester	9.80 (0.69)	96.16
	4/C sildenafil		
5a. All TNFi bDMARDs can be used throughout pregnancy.	2a/B all TNFi bDMARDs	9.56 (0.96)	92.00

(continued on next page)

Table 1 (Continued)

		Level of agreement	
		Mean (SD)	% with scores ≥8
<b>5b.</b> The following non-TNFi bDMARDs may be used if needed to effectively control maternal disease: abatacept, anakinra, belimumab, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab.	2b/B-4/C for these non-TNFi bDMARDs: 4/C abatacept (anti-T cell) 4/C anakinra (IL-1i) 4/C belimumab (anti-B cell) 4/C canakinumab (IL-1i) 4/C ixekizumab (IL-17i) 4/C rituximab (anti-B cell) 4/C sarilumab (IL-6i) 4/C secukinumab (IL-17i) 4/C tocilizumab (IL-6i) 2b/B ustekinumab (IL-12/23i)	9.29 (1.19)	95.84
<b>5c.</b> Very limited or no data are available on safe use in pregnancy for anifrolumab, eculizumab, guselkumab, mepolizumab, and risankizumab. These drugs should only be used during pregnancy if no other pregnancy-compatible medication can effectively control maternal disease.	5/D anifrolumab (IFNAR1i) 4/C eculizumab (C5i) 5/D guselkumab (IL-23i) 4/C mepolizumab (IL-5i) 5/D risankizumab (IL-23)	9.76 (0.51)	100
<b>5d.</b> Nonlive vaccines can be administered to all infants after exposure to any bDMARD during pregnancy. Administration of live-attenuated vaccines during the first 6 mo after delivery is dependent upon timing of maternal exposure to bDMARDs during pregnancy, transplacental passage of the bDMARD and type of the vaccine. <sup>a,b</sup>	2b/B <sup>a</sup> - 5/D <sup>b</sup>	9.40 (1.33)	85.18
<b>6.</b> Drugs for which there are insufficient safety data on use in pregnancy should be avoided until further evidence is available. This applies to apremilast, avacopan, baricitinib, bosentan, filgotinib, leflunomide, mepacrine, tofacitinib, upadacitinib, and voclosporin.	5/D apremilast 5/D avacopan 5/D baricitinib 5/D bosentan 5/D filgotinib 2b/B leflunomide: discontinue 5 half-lives (3.5 mo) before pregnancy or use accelerated drug elimination procedure (eg, cholestyramine) 4/C mepacrine 4/C tofacitinib 5/D upadacitinib 5/D voclosporin	9.74 (0.65)	100
<b>II. Antirheumatic drugs during lactation</b>			
<b>1.</b> csDMARDs and other drugs used in rheumatology practice that are compatible with breastfeeding include azathioprine or mercaptopurine, celecoxib, chloroquine, colchicine, cyclosporine, hydroxychloroquine, IVIG, IV methylprednisolone pulses, nonselective NSAIDs (eg, ibuprofen), prednisone and prednisolone, sulfasalazine, and tacrolimus.	2a/B azathioprine, mercaptopurine 4/C celecoxib 4/C chloroquine 2a/B colchicine 2a/B cyclosporine 2a/B hydroxychloroquine 2a/B IVIG 2a/B IV methylprednisolone pulses 2a/B nonselective NSAIDs (eg, ibuprofen) 2a/B prednisone, prednisolone 2a/C sulfasalazine 2a/B tacrolimus	9.73 (0.60)	100

(continued on next page)

Table 1 (Continued)

		Level of agreement	
		Mean (SD)	% with scores $\geq 8$
2. Minimal transfer into breast milk and limited systemic absorption by the breastfed child has been shown for bDMARDs due to their physicochemical and pharmacokinetic properties. Continuation of TNFi bDMARDs and non-TNFi bDMARDs should be considered compatible with breastfeeding.	2a/B all TNFi bDMARDs	9.69 (0.54)	100
	2a/B-5/D non-TNFi bDMARDs:		
	4/C abatacept (anti-T cell)		
	2a/B anakinra (IL-1i)		
	5/D anifrolumab (IFNAR1i)		
	4/C belimumab (anti-B cell)		
	2a/B canakinumab (IL-1i)		
	5/D eculizumab (C5i)		
	5/D guselkumab (IL-23i)		
	5/D ixekizumab (IL-17i)		
	5/D mepolizumab (IL-5i)		
	5/D risankizumab (IL-23i)		
	2a/B rituximab (anti-B cell)		
	4/C sarilumab (IL-6i)		
	5/D secukinumab (IL-17i)		
4/C tocilizumab (IL-6i)			
2a/B ustekinumab (IL-12/23i)			
3. Drugs with limited or no data on breastfeeding			
3a. Since the following drugs have very low levels in breast milk and show no evidence of harm in breastfed infants, they may be considered during breastfeeding if no alternative drug compatible with breastfeeding can be used: bosentan, sildenafil, and methotrexate $\leq 25$ mg weekly.	4/C bosentan, sildenafil	8.85 (2.26)	85.18
	4/C methotrexate $\leq 25$ mg weekly		
3b. The following drugs should be avoided in breastfeeding women and alternative drugs should be considered: apremilast, avacopan, baricitinib, cyclophosphamide, etoricoxib, filgotinib, iloprost, leflunomide, mycophenolate, tofacitinib, upadacitinib, and voclosporin.	5/D apremilast	9.59 (0.93)	96.30
	5/D avacopan		
	5/D baricitinib		
	4/D cyclophosphamide		
	5/D etoricoxib		
	5/D filgotinib		
	5/D iloprost		
	5/D leflunomide		
	5/D mycophenolate		
	4/D tofacitinib		
	5/D upadacitinib		
5/D voclosporin			

(continued on next page)

Table 1 (Continued)

		Level of agreement	
		Mean (SD)	% with scores $\geq 8$
<b>III. Antirheumatic drugs in male patients</b>			
1. Treatment with the following drugs has not demonstrated a clinically relevant impact on offspring outcome and can be continued in male patients trying to conceive. This applies to azathioprine or mercaptopurine, colchicine, cyclosporine, hydroxychloroquine and chloroquine, IVIG, leflunomide, methotrexate $\leq 25$ mg/week, mycophenolate, NSAIDs, prednisone and prednisolone, sildenafil, sulfasalazine, tacrolimus, TNFi bDMARDs, and non-TNFi bDMARDs <sup>c</sup> .	2b/B azathioprine, mercaptopurine	9.48 (1.04)	96.00
	2c/C colchicine		
	2b/B cyclosporine		
	2c/C hydroxychloroquine, chloroquine		
	5/D IVIG		
	2c/C leflunomide		
	2b/C methotrexate $\leq 25$ mg/wk		
	2b/C mycophenolate		
	2b/C NSAIDs		
	2b/B prednisone, prednisolone		
	4/C sildenafil		
	2b/C sulfasalazine: may have a reversible impact on sperm quality; if conception is delayed; consider stopping along with investigation of other causes of infertility		
	2b/B tacrolimus		
	1b/B all TNFi bDMARDs		
	2b/C-5/D non-TNFi bDMARDs <sup>c</sup> :		
	4/C abatacept (anti-T cell)		
	4/C anakinra (IL-1i)		
5/D belimumab (anti-B cell)			
4/C canakinumab (IL-1i)			
4/C ixekizumab (IL-17i)			
4/C rituximab (anti-B cell)			
5/D sarilumab (IL-6i)			
4/C secukinumab (IL-17i)			
4/C tocilizumab (IL-6i)			
2b/C ustekinumab (IL-12/23i)			
2b/B cyclophosphamide	9.88 (0.43)	100	
2. Cyclophosphamide is associated with a dose-related potential risk for irreversible infertility. Male patients should be counselled about options for fertility preservation before starting treatment.			

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Table 1 (Continued)

		Level of agreement	
		Mean (SD)	% with scores $\geq 8$
3. Limited or no data are available on the impact of male treatment with the following drugs: anifrolumab, apremilast, avacopan, baricitinib, bosentan, ecuzumab, filgotinib, guselkumab, mepolizumab, risankizumab, tofacitinib, upadacitinib, and voclosporin. Consider switching to an alternative antirheumatic medication in male patients trying to conceive.	5/D anifrolumab	9.23 (1.30)	92.31
	5/D apremilast		
	5/D avacopan		
	5/D baricitinib		
	5/D bosentan		
	5/D ecuzumab		
	1/B-4/C filgotinib: no negative impact on sperm quality, but very limited data on pregnancy outcome		
	5/D guselkumab		
	5/D mepolizumab		
	5/D risankizumab		
	4/C tofacitinib		
	5/D upadacitinib		
	5/D voclosporin		

anti-B cell, B-cell-targeted therapy; anti-T cell, T-cell costimulation modulator; BCG, Bacillus Calmette–Guérin; bDMARD, biologic disease-modifying antirheumatic drug; C5i, complement protein C5 inhibitor; COX, cyclooxygenase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; ILi, interleukin inhibitor; IFNAR1i, interferon  $\alpha/\beta$  receptor subunit 1 inhibitor; IV, intravenous; IVIG, intravenous immunoglobulin; LoE, level of evidence; GoR, grade of recommendation; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TNFi, tumour necrosis factor.

<sup>a</sup> Rotavirus vaccination can be administered according to the vaccination schedule in infants with *in utero* exposure to any TNFi bDMARD (LoE/GoR: 2b/B). BCG vaccination should be delayed for 6 months in infants with *in utero* exposure to TNFi bDMARDs with transplacental transfer during the second half of pregnancy (ie, adalimumab, golimumab, and infliximab after gestational week 20; etanercept after gestational week 32) (LoE/GoR: 2b/B). Certolizumab has minimal to no transplacental transfer and does not require any alteration to the infant vaccination schedule (LoE/GoR: 2b/B).

<sup>b</sup> Due to limited data on live-attenuated vaccines in infants exposed to non-TNFi bDMARDs during the second and third trimesters, live vaccines should be delayed for 6 months (LoE/GRADE: 4/C-5/D).

<sup>c</sup> Statement III/1 (drugs in male patients) refers to the following non-TNFi bDMARDs: abatacept, anakinra, belimumab, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab.

**Table 2**  
**Antirheumatic drugs in pregnancy**

Drugs compatible with pregnancy		Drugs may be used if needed to effectively control maternal disease		Drugs to treat severe, refractory maternal disease, or if no alternative medication can be used		Drug to be discontinued prior to conception due to teratogenicity		Drugs that should be avoided due to insufficient data	
Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR
hydroxychloroquine (HCQ) chloroquine (CQ)	2a/B HCQ 2c/B CQ	IL12/23i: ustekinumab	2b/B	IV methylprednisolone	4/C	cyclophosphamide <sup>a</sup>	2a/B	apremilast	5/D
sulfasalazine	2a/B	IL-6i: tocilizumab sarilumab	4/C	IVIG	3b/C	mycophenolate <sup>a</sup>	2a/B	avacopan	5/D
azathioprine 6-mercaptopurine	2a/B	IL-1i: anakinra canakinumab	4/C	sildenafil	4/C	methotrexate	2a/B	JAKi: tofacitinib, baricitinib, upadacitinib, filgotinib	4/C-5/D
cyclosporine (CyC) tacrolimus (TAC)	2a/B CyC 2b/B TAC	IL17i: secukinumab, ixekizumab	4/C	C5i: eculizumab	4/C			bosentan	5/D
colchicine	2b/B	anti-T cell: abatacept	4/C	IL-5i: mepolizumab	4/C			leflunomide (stop 5 half- lives prior to conception or washout)	2b/B
TNFi: adalimumab certolizumab etanercept golimumab infliximab	2a/B	anti-B cell: rituximab belimumab	4/C	IL-23i: guselkumab risankizumab	5/D			voclosporin	5/D
NSAIDs <sup>b</sup> prefer ibuprofen (IBU), diclofenac (DIC); (only intermittent use, stop after 28 GW)	2a/B IBU, DIC 2b/C COX2i			IFNAR1i: anifrolumab	5/D				
prednisone, prednisolone <sup>b</sup> (aiming at ≤ 5 mg/d)	2a/B								

anti-B cell, B-cell-targeted therapy; anti-T cell, T-cell costimulation modulator; C5i, complement protein C5 inhibitor; COX2i, cyclooxygenase 2 inhibitor; CyC, cyclosporine; GoR, grade of recommendation; GW, gestational week; ILi, interleukin inhibitor; IFNAR1i, interferon  $\alpha/\beta$  receptor subunit 1 inhibitor; IV, intravenous; IVIG, intravenous immunoglobulin; JAKi, Janus kinase inhibitor; LoE, level of evidence; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumour necrosis factor.

<sup>a</sup>Can be considered in severe organ- or life-threatening disease during second and third trimester: cyclophosphamide (LoE/GoR 4/C), mycophenolate (LoE/GoR 4/D).

<sup>b</sup>Restrictive use recommended: can be considered if needed to control disease activity.

**Table 3**  
**Antirheumatic drugs in lactation**

Drugs compatible with breastfeeding		Drugs may be considered in breastfeeding if no alternative medication can be used		Drugs to be avoided in breastfeeding due to insufficient data			
Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR		
NSAID: preferential use of ibuprofen (IBU) and celecoxib (CEL)	2a/B IBU 4/C CEL	IL12/23i: ustekinumab	2a/B	bosentan sildenafil	4/C	apremilast	5/D
prednisone, prednisolone IV methylprednisolone	2a/B	IL-6i: tocilizumab, sarilumab	4/C	methotrexate ≤25 mg weekly	4/C	avacopan	5/D
hydroxychloroquine (HCQ) chloroquine (CQ)	2a/B HCQ 4/C CQ	IL-1i: anakinra, canakinumab	2a/B			cyclophosphamide	4/D
sulfasalazine	2a/C	IL17i: secukinumab ixekizumab	5/D			etoricoxib	5/D
azathioprine 6-mercaptopurine	2a/B	IL-23i: guselkumab risankizumab	5/D			iloprost	5/D
cyclosporine tacrolimus	2a/B 2a/B	IFNAR1i: anifrolumab	5/D			JAKi: tofacitinib (TOF), baricitinib, upadacitinib, filgotinib	4/D (TOF), others 5/D
IVIG	2a/B	IL-5i: mepolizumab	5/D			leflunomide	5/D
colchicine	2a/B	C5i: eculizumab	5/D			mycophenolate	5/D
TNFi: adalimumab certolizumab etanercept golimumab infliximab	2a/B	anti-T cell: abatacept	4/C			voclosporin	5/D
		anti-B cell: rituximab (RTX) belimumab (BEL)	2a/B RTX 4/C BEL				

anti-B cell, B-cell-targeted therapy; anti-T cell, T-cell costimulation modulator; C5i, complement protein C5 inhibitor; GoR, grade of recommendation; ILi, interleukin inhibitor; IFNAR1i, interferon  $\alpha/\beta$  receptor subunit 1 inhibitor; IV, intravenous; IVIG, intravenous immunoglobulin; JAKi, Janus kinase inhibitor; LoE, level of evidence; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumour necrosis factor.

**Table 4**  
**Antirheumatic drugs in male patients planning to conceive**

Drugs compatible in male patients trying to conceive				Drugs with limited or no data in male patients, consider alternative medication		Drug to be discontinued in male patients before conception	
Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR	Drug	LoE/GoR
NSAIDs	2b/C	TNFi: adalimumab certolizumab etanercept golimumab infliximab	1b/B	JAKi: filgotinib (FIL), tofacitinib (TOF), baricitinib (BAR), upadacitinib (UPA)	1/B-4/C FIL** 4/C TOF 5/D BAR, UPA	cyclophosphamide	2b/B
prednisone, prednisolone	2b/B	IL12/23i: ustekinumab	2b/C	apremilast	5/D		
hydroxychloroquine (HCQ) chloroquine (CQ)	2c/C	IL-6i: tocilizumab (TOC) sarilumab (SAR)	4/C TOC 5/D SAR	avacopan	5/D		
sulfasalazine*	2b/C	IL-1i: anakinra, canakinumab	4/C	bosentan	5/D		
methotrexate ≤25 mg weekly	2b/C	IL17i: secukinumab ixekizumab	4/C	voclosporin	5/D		
leflunomide	2c/C	anti-T cell: abatacept	4/C	IL-23i: guselkumab risankizumab	5/D		
azathioprine 6-mercaptopurine	2b/B	Anti-B cell: rituximab (RTX) belimumab (BEL)	4/C RTX 5/D BEL	IFNAR1i: anifrolumab	5/D		
cyclosporine tacrolimus	2b/B	IVIG	5/D	IL-5i: mepolizumab C5i: eculizumab	5/D		
mycophenolate	2b/C						
colchicine	2c/C						
sildenafil	4/C						

\*may have a reversible impact on sperm quality; if conception is delayed, consider stopping along with investigation of other causes of infertility

\*\*no negative impact on sperm quality, but very limited data on pregnancy outcome

anti-B cell, B-cell-targeted therapy; anti-T cell, T-cell costimulation modulator; C5i, complement protein C5 inhibitor; COX-2i: cyclooxygenase-2 inhibitor; GoR: grade of recommendation; ILi, interleukin inhibitor; IFNAR1, interferon  $\alpha/\beta$  receptor subunit 1 inhibitor; LoE, level of evidence; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor.

<sup>a</sup>No negative impact on sperm quality but very limited data on pregnancy outcome.

<sup>b</sup>May have a reversible impact on sperm quality; if conception is delayed, consider stopping along with investigation of other causes of infertility.

≤400 mg, which should be favoured over chloroquine [13,18–20].

In women with normal thiopurine metabolism (eg, normal thiopurine methyltransferase activity), azathioprine can be used at daily doses up to 2 mg/kg throughout pregnancy [1].

Cyclosporine and tacrolimus can be used during pregnancy at the lowest effective dose, which may be monitored by trough levels [1,14,15].

Sulfasalazine can be continued at doses up to 2 g/d throughout pregnancy [1,11]. Since sulfasalazine inhibits folate absorption, concomitant daily folic acid supplementation is recommended [21–23].

Colchicine is compatible with pregnancy and can be used at doses of 1 to 2 mg/d [16].

**2. Cyclophosphamide, methotrexate, and mycophenolate are teratogenic and should be discontinued before pregnancy.**

Cyclophosphamide, methotrexate, and mycophenolate are proven embryotoxic and teratogenic drugs, meaning that exposure during a vulnerable period within the first trimester of pregnancy can lead to miscarriage or major birth defects [1,24,25]. Teratogenic drugs usually induce a pattern of malformation; however, this may not be the case with low-dose methotrexate [24–26]. Patients receiving cyclophosphamide, methotrexate, and mycophenolate should use effective contraception, and in case of family planning, the drugs should be discontinued before conception (methotrexate: 1-3 months; mycophenolate: 1.5 months; cyclophosphamide: 3 months) [1,27].

**3. Nonsteroidal anti-inflammatory drugs (NSAIDs), prednisone, and prednisolone can be considered during pregnancy if needed to control disease activity. Adding or**

**switching pregnancy-compatible csDMARDs or biologic disease-modifying antirheumatic drugs (bDMARDs) should be considered if needed to control active disease.**

Active rheumatic disease during pregnancy is a known risk factor for both maternal and foetal adverse health outcomes and should be treated immediately. NSAIDs and glucocorticoids can be used if needed to control signs and symptoms of active disease in pregnancy. However, recent evidence about dose- and time-dependent caveats has emerged that supports more restricted use of these drugs in the context of pregnancy. To control active disease, glucocorticoid- and NSAID-sparing strategies should be considered by adding or switching pregnancy-compatible csDMARDs (see point 1) or bDMARDs (see point 5).

**3 a. In pregnancy, NSAIDs should only be used intermittently and stopped after 28 weeks of gestation. Due to limited evidence on selective COX-2 inhibitors, nonselective NSAIDs with a short half-life (eg, ibuprofen) are preferred. Discontinuation of NSAIDs should be considered if there is difficulty in conceiving.**

For early pregnancy exposure to NSAIDs, data show no evidence of increased risk of miscarriage or teratogenicity [1,28,29]. Most reassuring data are available for ibuprofen, followed by diclofenac, whereas data for COX-2 inhibitors are limited [28,29]. Regarding the use of NSAIDs in the second trimester, current evidence shows that short-term use (7-10 days) does not appear to pose substantial risks for the foetus, with most data being available for ibuprofen [30–32]. As safety data on NSAIDs in the second trimester indicate that foetal adverse effects depend on exposure time, treatment duration, dosage, and intensity of prostaglandin inhibition, the TF favours nonselective NSAIDs with a short half-life, eg, ibuprofen, in the lowest effective dose for a short time (7-10 days) [31]. NSAIDs

should be restricted to the first and second trimester and discontinued after gestational week (GW) 28 (end of the second trimester), since the sensitivity to NSAID-related risks for the foetus increases in late pregnancy, eg, oligohydramnios or narrowing/occlusion of the foetal ductus arteriosus [1,30,31]. NSAIDs can interfere with ovulation, as this process depends on prostaglandins. Continuous periovulatory exposure to NSAIDs can induce luteinised unruptured follicle (LUF) syndrome and thus reduce a woman's fecundability [33,34]. The TF recommends that women with difficulty conceiving should consider discontinuing NSAIDs.

**3b. In pregnancy, prednisone and prednisolone should be tapered when possible to a maintenance dose of  $\leq 5$  mg/d and, when possible, withdrawn. The use of higher dosages should be weighed against the risk of maternal-foetal complications.**

Prednisone and prednisolone are not associated with an increased rate of major birth defects and can be considered during pregnancy if needed to control active disease [1,35–37]. However, due to dose-related potential risks for the mother and foetus, use in pregnancy warrants careful consideration. Adverse effects of glucocorticoid treatment during pregnancy over a prolonged period at higher doses may comprise pregnancy-associated osteoporosis, gestational diabetes, serious maternal infections, and preterm birth, whereas daily doses  $\leq 5$  mg are associated with low risk [3,38–43]. Follow-up of exposed children showed conflicting results with regard to infection rates but normal developmental milestones and no increased risk for insulin resistance [35,36,44]. In view of the current evidence, the TF recommends a restrictive use of oral glucocorticoids in pregnant women.

**4. In severe, refractory maternal disease during pregnancy, intravenous (IV) methylprednisolone pulses, pregnancy-compatible csDMARDs and/or bDMARDs, IV immunoglobulin (IVIG), sildenafil, or, in the second and third trimester, cyclophosphamide or mycophenolate can be considered.**

This statement addresses treatment options for severe, refractory, or organ- or life-threatening maternal disease during pregnancy. The safest options in this context are IV methylprednisolone pulses, csDMARDs (see point 1), bDMARDs (see point 5), IVIG, and sildenafil [1,45–48]. If needed, combinations of these latter drugs or drug-groups may be recommended. If there is no other available option, cyclophosphamide or mycophenolate in the second or third trimester of pregnancy might be justified for the treatment of organ- or life-threatening maternal disease [1,49–52].

**5. For bDMARD use in pregnancy, individual drug effectiveness and transplacental transfer should be taken into consideration.**

Two important aspects should be considered with regard to the use of bDMARDs in pregnancy. First, the effectiveness of the biologic in achieving or maintaining inactive disease versus the risk of disease worsening in absence of the biologic should be evaluated. Second, immunoglobulin G (IgG)-based biologics undergo the same neonatal Fc receptor (FcRn)-mediated transplacental transfer as natural maternal IgG antibodies, starting around week 20 and progressively increasing until term [53]. The binding affinity to placental FcRn is most efficient for monoclonal IgG1 antibodies (eg, infliximab [IFX], adalimumab [ADA], golimumab [GOL], rituximab [RTX]), low for Fc fusion proteins (etanercept [ETA], abatacept [ABA]), and insignificant for Fc-free molecules (certolizumab [CZP]) [54]. Accordingly, biologics used

throughout pregnancy may lead to neonatal drug levels exceeding maternal levels for monoclonal IgG1 antibodies (IFX, ADA, and GOL), while neonatal drug levels are low for Fc fusion proteins (ETA and ABA), and minimal to undetectable for Fc-free molecules (CZP) [17,55,56]. Anakinra does not contain any immunoglobulin structures and is therefore not subject to FcRn-mediated transplacental transfer. In infants with detectable levels of IFX or ADA at birth, the mean time to drug clearance is 4 to 7 months [17,57].

Given that *in utero* exposure to bDMARDs in the second half of pregnancy could affect planning of live vaccination in the infant (see point 5d), the following approach ensures no to minimal neonatal drug levels [1,58]:

- stopping whole IgG1-based biologics (eg, IFX, ADA) by GW 20
- stopping Fc fusion proteins (eg, ETA) by GW 30 to 32
- continuing Fc-free molecules (CZP) throughout pregnancy

**5a. All tumour necrosis factor inhibitor (TNFi) bDMARDs can be used throughout pregnancy.**

Data on the safety of TNFi bDMARDs in pregnancy has substantially increased since the EULAR 2016 PtC. Current evidence, including our meta-analysis, indicates that TNFi bDMARDs (IFX, ADA, GOL, ETA, and CZP) are not associated with an increased risk of congenital malformations, miscarriage, or any other adverse pregnancy outcomes. Similar results were obtained by other meta-analyses published previously [59–61]. With regard to the impact of *in utero* exposure to TNFi any time during pregnancy or in the third trimester, the evidence showed no increased risk of serious infections in children within the first year of life [4].

**5b. The following non-TNFi bDMARDs may be used if needed to effectively control maternal disease: abatacept, anakinra, belimumab, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab.**

Current evidence indicates that non-TNFi bDMARDs do not appear to increase the rate of adverse pregnancy outcomes compared to background frequencies in the general population [1,62]. However, for most of these biologics, the LoE is weaker than for TNFi. Limited data do not raise concerns about the impact of *in utero* exposure to non-TNFi bDMARDs (anakinra, canakinumab, ustekinumab, RTX, belimumab) on infant outcome [63–67]. Of note, administration of anti-B cell agents (RTX, belimumab) in the second half of pregnancy could result in transient B cell depletion or other cytopenias in the neonate but without serious infections and with recovery of B cells within 6 months [63,65,66,68–70].

**5c. Very limited or no data are available on safe use in pregnancy for anifrolumab, eculizumab, guselkumab, mepolizumab, and risankizumab. These drugs should only be used during pregnancy if no pregnancy-compatible medication can effectively control maternal disease.**

No concern regarding drug-related adverse pregnancy outcomes was seen among bDMARDs with very limited data (mepolizumab, eculizumab) and are not expected for those with no data (anifrolumab, guselkumab, risankizumab) [71–75]. In view of the scarce data available, a risk-benefit assessment should be applied.

**5d. Nonlive vaccines can be administered to all infants after exposure to any bDMARD during pregnancy. Administration of live-attenuated vaccines during the first 6 months after delivery is dependent upon timing of maternal**

### exposure to bDMARDs during pregnancy, transplacental passage of the bDMARD, and type of vaccine.

With regard to nonlive vaccinations during the first year of life in children after *in utero* exposure to bDMARDs, current evidence indicates no increased rates of serious adverse events and an adequate immune response [76]. The TF concluded that nonlive vaccines can be administered to all infants with prenatal exposure to any bDMARD according to the normal schedule in their health care setting.

The vaccination schedule during the first 12 months may include the live-attenuated vaccines Bacille Calmette–Guérin (BCG) and rotavirus. Regarding BCG, there are rare cases of fatal disseminated BCG [5 of 215] in infants exposed to TNFi agents (most frequently IFX) *in utero* during the second half of pregnancy following BCG vaccination within the first 6 months of age [77,78]. BCG vaccination should be delayed for 6 months in infants exposed *in utero* to TNFi bDMARDs with transplacental transfer during the second half of pregnancy (ie, IFX, ADA, GOL after GW 20; ETA after GW 32). CZP has minimal to no transplacental transfer and does not require any alteration to the infant vaccination schedule [79].

With regard to the live-attenuated rotavirus vaccine, evidence indicates that infants exposed to TNFi bDMARDs *in utero* are not at increased risk of adverse events compared to unexposed children [77,80,81]. Thus, rotavirus vaccination can be administered according to the usual vaccination schedule in infants with *in utero* exposure to any TNFi bDMARDs.

Due to limited data on live-attenuated vaccines in infants exposed to non-TNFi bDMARDs during the second and third trimesters, live vaccines should be delayed for 6 months.

### 6. Drugs for which there are insufficient safety data on use in pregnancy should be avoided until further evidence is available. This applies to apremilast, avacopan, baricitinib, bosentan, filgotinib, leflunomide, mepacrine, tofacitinib, upadacitinib, and voclosporin.

For these drugs, the evidence of safety during pregnancy is insufficient, rather than evidence of harm. In patients planning a pregnancy, these drugs should be avoided or replaced by pregnancy-compatible csDMARDs (see point 1) or bDMARDs (see point 5). Data on leflunomide and its active metabolite teriflunomide do not indicate a major teratogenic effect in humans; however, the proportion of patients who underwent a drug washout was either unknown or between 32% and 95% [82–86]. In light of the current evidence, leflunomide should either be discontinued 5 half-lives (3.5 months) before pregnancy or a drug washout procedure (eg, cholestyramine) performed.

#### II Antirheumatic drugs during lactation

1. csDMARDs and other drugs used in rheumatology practice that are compatible with breastfeeding include azathioprine or mercaptopurine, celecoxib, chloroquine, colchicine, cyclosporine, hydroxychloroquine, IVIG, IV methylprednisolone pulses, nonselective NSAIDs (eg, ibuprofen), prednisone and prednisolone, sulfasalazine, and tacrolimus.

In keeping with the previous EULAR version, these aforementioned csDMARDs and anti-inflammatory medications are compatible with breastfeeding and should be continued [1,87].

With regard to IV methylprednisolone pulses (1000 mg), the maximum level in breast milk occurs within 2 hours after the dose and falls exponentially to very low levels; therefore, a delay of 2 to 4 hours before breastfeeding could limit the infant's exposure [88,89]. Due to the safety data and its extremely low excretion into breast milk, the NSAID ibuprofen should be preferred in lactating mothers [87]. Very rarely, pharmacogenetic variants

(eg, deficiency of glucose-6-phosphate dehydrogenase or thio-purine methyltransferase) might lead to drug-related side effects in breastfed infants [1,90].

### 2. Minimal transfer into breast milk and limited systemic absorption by the breastfed child have been shown for bDMARDs due to their physicochemical and pharmacokinetic properties. Continuation of TNFi bDMARDs and non-TNFi bDMARDs should be considered compatible with breastfeeding.

Contrary to the 2016 PtC, the TF decided to consider all bDMARDs (TNFi bDMARDs and non-TNFi bDMARDs) as compatible with breastfeeding. The reasons for this decision were 2 general characteristics of all bDMARDs. First, biologics are mostly IgG1-based proteins with molecular weights from about 17,000 (eg, anakinra) to 150,000 Da (eg, IFX), which impede their passive diffusion through the intercellular space between mammary cells into breast milk [91,92]. Second, they have negligible oral bioavailability [1,92]. Accordingly, the SLR revealed that all bDMARDs are undetectable or appear in only minimal amounts in breast milk. In infants of mothers starting treatment during lactation, no serum concentrations of bDMARDs were detectable [93–95]. The body of evidence on various bDMARDs without serious adverse events in breastfed infants supports their continuation during breastfeeding.

### 3a. Drugs with limited or no data on breastfeeding: Since the following drugs have very low levels in breast milk and show no evidence of harm in breastfed infants, they may be considered during breastfeeding if no alternative drug compatible with breastfeeding can be used: bosentan, sildenafil, and methotrexate $\leq 25$ mg weekly.

The TF intensely discussed the very limited data on bosentan, sildenafil, and methotrexate ( $\leq 25$  mg weekly) in lactating women and agreed that the risk may be acceptable during breastfeeding if no alternative drug compatible with breastfeeding can be used, in view of the very low amounts excreted into breast milk and the absence of reported harm in breastfed infants [1,87].

### 3b. Drugs with limited or no data on breastfeeding: The following drugs should be avoided in breastfeeding women and alternative drugs should be considered: apremilast, avacopan, baricitinib, cyclophosphamide, etoricoxib, filgotinib, iloprost, leflunomide, mycophenolate, tofacitinib, upadacitinib, and voclosporin.

Insufficient data rather than the evidence of infant harm is the reason to avoid apremilast, avacopan, etoricoxib, iloprost, all Janus kinase inhibitors (JAKis), leflunomide, mycophenolate, and voclosporin in breastfeeding women [87]. As for cyclophosphamide, 2 cases of bone marrow suppression in infants exposed via breast milk have previously been described [87].

#### III. Antirheumatic drugs in male patients

1. Treatment with the following drugs has not demonstrated a clinically relevant impact on offspring outcome and can be continued in male patients trying to conceive. This applies to azathioprine or mercaptopurine, colchicine, cyclosporine, hydroxychloroquine and chloroquine, IVIG, leflunomide, methotrexate  $\leq 25$  mg/wk, mycophenolate, NSAIDs, prednisone and prednisolone, sildenafil, sulfasalazine, tacrolimus, TNFi bDMARDs, and non-TNFi bDMARDs (see Table 1).

Given that high disease activity itself may impair male fertility [96–99], controlling rheumatic diseases with compatible drugs is the best strategy. Current evidence suggests that all the above drugs have no negative impact on birth outcome and can be continued in male patients planning to conceive. This also

applies to drugs that would be discontinued in women before attempting pregnancy such as methotrexate, leflunomide, and mycophenolate, since data in men showed no evidence of an increased risk for birth defects [85,100–105]. Sulfasalazine may have a reversible negative impact on sperm quality but does not increase adverse pregnancy outcomes [11,100,101]. Because oxidative stress is thought to be the possible mechanism, adding antioxidants (eg, folic acid) might be beneficial for men taking sulfasalazine and trying to conceive [106]. The TF agreed that sulfasalazine can be continued in men, but if conception is delayed, discontinuation of this drug should be considered along with investigating other causes of infertility.

**2. Cyclophosphamide is associated with a dose-related potential risk for irreversible infertility. Male patients should be counselled about options for fertility preservation before starting treatment.**

There is clear evidence that the alkylating agent cyclophosphamide exerts a dose-related negative impact on spermatogenesis and secondary androgen deficiency [100,101,107]. A dose threshold of  $\geq 4000$  mg/m<sup>2</sup> is likely to result in permanent azoospermia, whereas a dose threshold  $< 4000$  mg/m<sup>2</sup> might be associated with a lower risk of infertility [107]. Reproductive studies in rats have shown male-mediated teratogenicity, but data about the impact of paternal cyclophosphamide therapy on pregnancy outcome in humans are too limited to draw conclusions [100,101]. The TF recommends counselling male patients about fertility preservations before starting treatment and to discontinue cyclophosphamide at least 3 months prior to attempting conception.

**3. Limited or no data are available on the impact of male treatment with the following drugs: anifrolumab, apremilast, avacopan, baricitinib, bosentan, eculizumab, filgotinib, guselkumab, mepolizumab, risankizumab, tofacitinib, upadacitinib, and voclosporin. Consider switching to an alternative antirheumatic medication in male patients trying to conceive.**

Although there is no evidence of an adverse effect on sperm quality for the JAKi filgotinib, there is limited data on birth outcomes after paternal drug exposure for tofacitinib and filgotinib and a lack of data for other JAKis [108,109]. Insufficient data rather than the evidence of infant harm as well as the potential risk of untreated disease were the reasons for the TF to consider switching these drugs to an alternative medication with more safety data on male fertility and offspring outcomes after paternal exposure.

## DISCUSSION

Since the publication of the 2016 EULAR PtC for use of anti-rheumatic drugs before pregnancy and during pregnancy and lactation, several studies have expanded our knowledge about drug safety in this field and allowed substantial updates of the previous version [1]. New data enabled us to elevate the LoE for several drugs. All recommendations are supported by expert consensus with high LoA. The updated version includes recommendations on the use of antirheumatic drugs in female and male patients planning a family and in pregnant and breastfeeding women.

The overarching principles of good counselling have been expanded and revised and are the key to ensure the best possible

outcomes for both the patient and infant [7]. Compared to the previous version [1], there are important changes. First is the more permissive use of bDMARDs in reproduction, pregnancy, and lactation. Among all biologics, TNFi bDMARDs are those with the highest LoE with regard to relatively safe pregnancy and infant outcomes. TNFi bDMARDs are also the most studied biologics in lactation and in male reproduction. The evidence for non-TNFi bDMARDs is more limited, less often compared to control groups, and often confounded by disease severity or comedication. Therefore, recommendations for biologics with limited or no data are also based on similarities of physiochemical and pharmacokinetic properties to TNFi bDMARDs. In this context, complete IgG-based biologics are assumed to have the same pattern of transplacental transport in the second half of pregnancy and low to minimal transfer into breast milk. Since treatment with biologics during late pregnancy could be influenced by the considerations of live vaccinations of *in utero* exposed infants, we included a new recommendation on vaccination of infants with *in utero* exposure to bDMARDs. In breastfeeding women, all bDMARDs are now considered as lactation-compatible drugs based on similar molecular size and pharmacokinetic properties [92]. A further approach in this direction is a novel risk assessment metric termed the “upper area under the curve ratio,” which overcomes the limited data on medication during breastfeeding by predicting breastfed infant risk based on drug characteristics and paediatric system parameters such as physiology and age-dependent factors [110].

Second, the current update recommends a more restrictive use of NSAIDs and oral glucocorticoids in women before and during pregnancy due to potential drug-mediated fetomaternal risks that are related to dose and treatment duration. Third, recommendations on the use of antirheumatic drugs in men planning a family are now included.

Despite progress over the past decade, we acknowledge that safety information for several antirheumatic drugs in male and female reproduction is still limited due to shortcomings of retrospectively collected data, or insufficient data [111]. To assess relative safety, the risk of a drug is compared with the background risk in the general population or, ideally, with the risk of an untreated disease. We also encourage referral to other evidence-based guidelines and recommendations on management and antirheumatic drugs from periconception to pregnancy and lactation [21,27,48,79,112]. In pregnancy, the best available evidence on drug safety derives from prospective cohort studies with unexposed disease controls and adjustment for important confounding factors such as disease severity and comedication. In lactation, well-performed pharmacokinetic studies can provide reassuring evidence of minimal infant exposure. More future research is needed, with points to be addressed listed in [Box 1](#).

The updated recommendations on antirheumatic drugs in reproduction, pregnancy, and lactation will help to improve the management and outcome of patients. Dissemination of the updated knowledge will be directed to national societies for rheumatology, internal medicine, gynaecology and obstetrics, family medicine, paediatrics, pharmacology, and national information services for teratology, as well as to patients. We encourage all clinicians and healthcare providers to implement these recommendations into their daily clinical practice.

### Box 1 Future research agenda

#### (A) General requirements for future research in the field of reproduction, pregnancy, and lactation

- To include pregnant patients in clinical trials and cohort studies whenever scientifically justified and ethically appropriate [111], especially if preclinical reproductive toxicity studies did not show any signals for increased risk of miscarriage/malformations
- To facilitate ethics procedures to collect data about both the mother and the child
- To apply innovative trial designs, eg, adaptive platform trial design assessing multiple interventions against a shared control group [111]
- To standardise study outcomes (eg, major birth defects among all pregnancies and major birth defects in live-born infants) and methods (eg, compare outcomes in disease-exposed versus disease-unexposed; adjust for confounding factors; provide the exact dates of drug exposure in pregnancy)
- To update and revise the summary of product characteristics and patient-leaflet with experts in the field to better assess the benefit-risk ratio and address it in lay language
- To re-evaluate the implementation of these EULAR recommendations in daily clinical practice

#### (B) Drugs in pregnancy

- To prospectively investigate or consolidate the safety of antirheumatic drugs in pregnancy
  - strengthen the safety profile of hydroxychloroquine using large databases
  - data on newer medications mentioned in section 1.6 (eg, JAKi and voclosporin) are needed
- To further analyse long-term follow-up data of children exposed to antirheumatic drugs *in utero* with regard to risk of infections, response to vaccination, and long-term developmental outcomes
  - more data regarding exposure to bDMARDs beyond GW 20 are needed (investigating the impact on the infant's immune system)
- To study developmental milestones of *in utero*-exposed children until school age

#### (C) Drugs in lactation

- To perform complete breastfeeding studies that include drug concentrations measured in maternal blood, breast milk, and infant blood plus follow-up of infants for drug-related adverse events
- To examine the safety of antirheumatic drugs with limited or no data in lactation mentioned in section II.3 (eg, methotrexate, JAKis, and voclosporin)
- To study the levels of maternal medication in the serum of breastfed premature infants and in neonates during the first 2 weeks postpartum (colostrum and transitional milk phases)

#### (D) Drugs in male patients

- To investigate sexual dysfunction, sperm quality, and reproductive hormones in males on antirheumatic drugs with limited or no data
- To analyse birth outcomes following paternal periconceptional exposure to antirheumatic drugs (eg, JAKis)
- To study long-term outcomes of children whose fathers used antirheumatic drugs during the periconception period

bDMARD, biologic disease-modifying antirheumatic drugs; EULAR, European Alliance of Associations for Rheumatology; GW, gestational week; JAKi, Janus kinase inhibitor.

## Competing interests

EULAR\_QoC012-Task force reports that financial support was provided by European Alliance of Associations for Rheumatology. The information regarding conflicts of interest of all authors can be provided by EULAR.

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## Acknowledgements

We are grateful to Monika Østensen for her unique pioneering work in this area and for approving the final version of the manuscript.

## Funding

This work was supported by the European League Against Rheumatism as project QoC012.

## Patient consent for publication

Not applicable.

## Ethics approval

Not applicable.

## Provenance and peer review

Not applicable.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.02.023.

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