RHEUMATOLOGY

Rheumatology 2016;55:1693–1697
doi:10.1093/rheumatology/kev404
Advance Access publication 10 January 2016

Guidelines

BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids

Julia Flint[1], Sonia Panchal[2], Alice Hurrell[3], Maud van de Venne[4], Mary Gayed[5], Karen Schreiber[6,7], Subha Arthanari[8], Joel Cunningham[3], Lucy Flanders[3], Louise Moore[9], Amy Crossley[10], Neetha Purushotham[3], Amisha Desai[5], Madeleine Piper[11], Mohamed Nisar[8], Munther Khamashta[6], David Williams[3], Caroline Gordon[12,13] and Ian Giles[1,3] on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group

Key words: rheumatic disease, pregnancy, breastfeeding, prescribing, corticosteroids, hydroxychloroquine, DMARDs, biologics

GUIDELINES

Executive Summary

Scope and purpose of the guideline

Need for guidelines

The prescribing of many drugs in pregnancy is complicated by a lack of knowledge regarding their compatibility leading to patient misinformation and withdrawal/denial of disease-ameliorating therapies. This situation should be avoided because active rheumatic disease is associated with adverse pregnancy outcomes [1] and there is growing evidence of drug safety in pregnancy.

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by the BSR to produce its guidance on prescribing drugs in pregnancy and breastfeeding. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

[1]Centre for Rheumatology Research, UCL Division of Medicine, University College London, London, [2]Department of Rheumatology, University Hospitals of Leicester, Leicester, [3]Womens Health, University College London Hospital, London, [4]Obstetrics and Gynaecology, Frimley Park Hospital, Surrey, [5]Department of Rheumatology, University Hospital Birmingham NHS Foundation Trust, Birmingham, [6]Department of Rheumatology, Guy's and St Thomas' NHS Foundation Trust, London, UK, [7]Department of Rheumatology, Copenhagen University Hospital, Rigshospitalet, Denmark, [8]Department of Rheumatology, Burton Hospitals NHS Trust, Burton-upon-Trent, [9]Rheumatic and Musculoskeletal Disease Unit, Our Lady's Hospice and Care Services, Dublin, Ireland, [10]Department of Rheumatology, University College London Hospital, London, [11]Department of Rheumatology, Aneurin Bevan University Health Board, Newport, UK, [12]Department of Rheumatology, Sandwell and West Birmingham Hospitals NHS Trust and [13]Division of Immunity and Infection, University of Birmingham, Birmingham, UK

Submitted 17 June 2015; revised version accepted 4 November 2015

Correspondence to: Ian Giles, Centre for Rheumatology Research, UCL Division of Medicine, Room 411, Rayne Institute, 5 University Street, London, UK. E-mail: i.giles@ucl.ac.uk

Objectives of the guideline

To provide evidence-based recommendations, which do not imply a legal obligation, for clinicians when prescribing anti-rheumatic drugs before/during pregnancy and breastfeeding that update previous recommendations [2, 3]. For recommendations on prescribing other drugs in pregnancy and breastfeeding see the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines part II [4].

Target audience

Health professionals directly involved in managing patients with rheumatic disease in the UK who are (or planning to become) pregnant and/or breastfeeding, men planning to conceive and patients who have accidentally conceived while taking these medications.

The areas the guideline does not cover

This guideline does not cover the management of infertility or the indications for these drugs in specific rheumatic diseases in pregnancy.

Key recommendations from the guidelines

Specific questions were considered in relation to each drug. Should it be stopped pre-conception? Is it compatible with pregnancy? Is it compatible with breastfeeding? Where possible, recommendations are made regarding compatibility with paternal exposure. These findings are summarized in Table 1. A description of evidence and full recommendations are given in the full guideline provided as supplementary data, available at *Rheumatology* Online.

Recommendations for corticosteroids in pregnancy and breastfeeding

(i) Prednisolone is compatible with each trimester of pregnancy [level of evidence (LOE) 1 ++, grade of recommendation (GOR) A, strength of agreement (SOA) 100%].
(ii) Prednisolone is compatible with breastfeeding (LOE 2−, GOR D, SOA 98.9%).
(iii) Prednisolone is compatible with paternal exposure (LOE 2+, GOR D, SOA 98.9%).
(iv) Methylprednisolone has rates of placental transfer similar to prednisolone with equivalent anti-inflammatory effects at 80% of prednisolone dose and would therefore be expected to be compatible with pregnancy, breastfeeding and paternal exposure (LOE 4, GOR D, SOA 93.7%).

Recommendations for HCQ in pregnancy and breastfeeding

(i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment and should be continued during pregnancy (LOE 1 ++, GOR A, SOA 100%).
(ii) HCQ is compatible with breastfeeding (LOE 4, GOR D, SOA 98.9%).
(iii) Men should not be discouraged from taking HCQ while trying to conceive (LOE 2−, GOR D, SOA 98.9%).

Recommendations for MTX in pregnancy and breastfeeding

(i) MTX at any dose should be avoided in pregnancy and stopped 3 months in advance of conception (LOE 2−, GOR D, SOA 100%).
(ii) In women treated with low-dose MTX within 3 months prior to conception, folate supplementation (5 mg/day) should be continued prior to and throughout pregnancy (LOE 1, GOR B, SOA 98.4%).
(iii) In the case of accidental pregnancy on low-dose MTX, the drug should be stopped immediately, folate supplementation (5 mg/day) continued and a careful evaluation of foetal risk carried out by local experts (LOE 4, GOR D, SOA 100%).
(iv) MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient outcome data (LOE 4, GOR D, SOA 100%).
(v) Based on limited evidence, low-dose MTX may be compatible with paternal exposure (LOE 2+, GOR D, SOA 95.8%).

Recommendations for SSZ in pregnancy and breastfeeding

(i) SSZ with folate supplementation (5 mg/day) is compatible throughout pregnancy (LOE 2+, GOR C, SOA 100%).
(ii) SSZ is compatible with breastfeeding in healthy, full-term infants (LOE 4, GOR D, SOA 100%).
(iii) Men taking SSZ may have reduced fertility. There is no evidence, however, that conception is enhanced by stopping SSZ for 3 months prior to conception unless conception is delayed >12 months when other causes of infertility should also be considered (LOE 3, GOR D, SOA 97.4%).

Recommendations for LEF in pregnancy and breastfeeding

(i) Based on limited evidence, LEF may not be a human teratogen but it is still not recommended in women planning pregnancy (LOE 2+, GOR C, SOA 100%).
(ii) Women on LEF considering pregnancy should stop and undergo cholestyramine washout before switching to alternative medication compatible with pregnancy (LOE 2+, GOR C, SOA 100%).
(iii) There is no human evidence of increased congenital abnormalities on LEF if washout is given. Therefore, if accidental conception occurs on LEF, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable (LOE 2+, GOR C, SOA 98.9%).
(iv) No data exist on excretion into breast milk, therefore breastfeeding is not recommended (LOE 4, GOR D, SOA 100%).
(v) Based on very limited evidence, LEF may be compatible with paternal exposure (LOE 4, GOR D, SOA 98.9%).

Table 1 Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
HCQ	Yes	Yes	Yes	Yes	Yes[a]
DMARDs					
MTX <20 mg/week	Stop 3 months in advance	No	No	No	Yes[a]
SSZ (with 5 mg folic acid)	Yes	Yes	Yes	Yes[b]	Yes[c]
LEF	Cholestyramine washout, no	No	No	No data	Yes[a]
AZA <2 mg/kg/day	Yes	Yes	Yes	Yes	yes
CSA	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
Tacrolimus	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
CYC	No	No[e]	No[e]	No	No
MMF	Stop 6 weeks in advance	No	No	No	Yes[a]
IVIG	Yes	Yes	Yes	Yes	Yes[a]
Anti-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes[a]	Yes[a]
Etanercept	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Adalimumab	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Certolizumab	Yes	Yes	Yes[a]	Yes[a]	No data
Golimumab	No data	No data	No data	No data	No data
Other biologics					
Rituximab	Stop 6 months in advance	No[f]	No	No data	Yes[a]
Tocilizumab	Stop 3 months in advance	No[f]	No	No data	No data[g]
Anakinra	No	No[f]	No	No data	No data[g]
Abatacept	No	No[f]	No	No data	No data[g]
Belimumab	No	No[f]	No	No data	No data[g]

For further information and caveats, see relevant recommendations and main text in executive summary and full guideline. [a]Data are limited. [b]In healthy full-term infants only. [c]Conception may be enhanced by stopping SSZ for 3 months prior to conception. [d]Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels. [e]Only consider in severe or life-/organ-threatening maternal disease. [f]Unintentional first trimester exposure is unlikely to be harmful. [g]Unlikely to be harmful.

Recommendations for AZA in pregnancy and breastfeeding

(i) AZA is compatible throughout pregnancy at ⩽2 mg/kg/day (LOE 2++, GOR B, SOA 100%).
(ii) AZA is compatible with breastfeeding (LOE 2−, GOR D, SOA 99.5%).
(iii) AZA is compatible with paternal exposure (LOE 2+, GOR D, SOA 100%).

Recommendations for CSA in pregnancy and breastfeeding

(i) CSA is compatible throughout pregnancy at the lowest effective dose (LOE 1, GOR B, SOA 100%).
(ii) Mothers on CSA should not be discouraged from breastfeeding (LOE 3, GOR D, SOA 100%).
(iii) Based on limited evidence, CSA is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Recommendations for tacrolimus in pregnancy and breastfeeding

(i) Tacrolimus is compatible throughout pregnancy at the lowest effective dose (LOE 2−, GOR D, SOA 99.5%).
(ii) Mothers on tacrolimus should not be discouraged from breastfeeding (LOE 3, GOR D, SOA 99.5%).
(iii) Based on limited evidence, tacrolimus is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.4%).

Recommendations for CYC in pregnancy and breastfeeding

(i) CYC is teratogenic and gonadotoxic, therefore it should only be considered in pregnancy in life-/organ-threatening maternal disease (LOE 2, GOR C, SOA 100%).

(ii) There is no evidence to recommend the use of CYC in breastfeeding (LOE 4, GOR D, SOA 100%).
(iii) Paternal exposure to CYC is not recommended (LOE 4, GOR D, SOA 98.4%).

Recommendations for MMF in pregnancy and breastfeeding

(i) MMF remains contraindicated during pregnancy (LOE 2−, GOR D, SOA 100%).
(ii) Treatment with MMF should be stopped at least 6 weeks before a planned pregnancy (LOE 3, GOR D, SOR 100%).
(iii) No data exist on excretion into breast milk, therefore breastfeeding is not recommended (LOE 4, GOR D, SOA 99.5%).
(iv) Based on very limited evidence, MMF is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Recommendations for IVIG in pregnancy and breastfeeding

(i) IVIG is compatible with pregnancy (LOE 1++, GOR A, SOA 100%).
(ii) IVIG is compatible with breastfeeding (LOE 4, GOR D, SOA 98.9%).
(iii) Based on maternal compatibility, IVIG is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Recommendations for anti-TNF medications in pregnancy and breastfeeding

(i) Infliximab (IFX) may be continued until 16 weeks and etanercept (ETA) and adalimumab (ADA) may be continued until the end of the second trimester (LOE 2−, GOR D, SOA 98.9%).
(ii) To ensure low/no levels of drug in cord blood at delivery, ETA and ADA should be avoided in the third trimester and IFX stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age (LOE 3, GOR D, SOA 98.9%).
(iii) Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis) (LOE 2−, GOR D, SOA 97.9%).
(iv) Golimumab is unlikely to be harmful in the first trimester (LOE 4, GOR D, SOA 97.9%)
(v) Women should not be discouraged from breastfeeding on TNFis, but caution is recommended until further information is available (LOE 3, GOR D, SOA 98.4%).
(vi) Based on limited evidence IFX, ETA and ADA are compatible with paternal exposure (LOE 2−, GOR D, SOA 98.9%).

Recommendations for rituximab (RTX) in pregnancy and breastfeeding

(i) RTX should be stopped 6 months before conception. Limited evidence has not shown RTX to be teratogenic and only second-/third-trimester exposure is associated with neonatal B cell depletion. Therefore, unintentional RTX exposure early in the first trimester is unlikely to be harmful (LOE 2−, GOR D, SOA 97.9%).
(ii) There are no data on RTX use in breastfeeding (SOA 100%).
(iii) Based on limited evidence, RTX is compatible with paternal exposure (LOE 2−, GOR D, SOA 98.4%).

Recommendations for tocilizumab (TCZ) in pregnancy and breastfeeding

(i) TCZ should be stopped at least 3 months before conception, but unintentional exposure early in the first trimester is unlikely to be harmful (LOE 3, GOR D, SOA 96.8%).
(ii) There are no data on TCZ use in breastfeeding (SOA 99.5%).
(iii) There are no data relating to paternal exposure to TCZ, but it is unlikely to be harmful (LOE 4, GOR D, SOA 97.9%).

Recommendations for anakinra in pregnancy and breastfeeding

(i) There is limited evidence on which to base a recommendation for anakinra in pregnancy, but unintentional exposure in the first trimester is unlikely to be harmful (LOE 2−, GOR D, SOA 96.8%).
(ii) There are no data on anakinra use in breastfeeding (SOA 100%).
(iii) There are no data relating to paternal exposure to anakinra, but it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Recommendations for abatacept (ABA) in pregnancy and breastfeeding

(i) There are insufficient data to recommend ABA in pregnancy. Unintentional exposure early in the first trimester is unlikely to be harmful (LOE 3, GOR D, SOA 98.9%).
(ii) There are no data on ABA use in breastfeeding (SOA 100%).
(iii) There are no data relating to paternal exposure to ABA, but it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Recommendations for belimumab (BEL) in pregnancy and breastfeeding

(i) There are insufficient data to recommend BEL in pregnancy. Unintentional exposure early in the first

trimester is unlikely to be harmful (LOE 3, GOR D, SOA 100%).

(ii) There are no data on BEL use in breastfeeding (SOA 100%).

(iii) There are no data relating to paternal exposure to BEL, but it is unlikely to be harmful (LOE 4, GOR D, SOA 98.9%).

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: K.S. has received educational support from Daiichi Sankyo. C.G. has undertaken consultancies and received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, Merck Serono and UCB, has been a member of speakers' bureau for GlaxoSmithKline, UCB and Lilly and has received research grant support from UCB, but none of these activities have been related to the use of any specific drug in pregnancy. L.M. has received support from AbbVie and Pfizer to attend education meetings and received participation honoraria from MSD. I.G. has received unit support from AbbVie, MSD, Roche, Bristol-Myers Squibb and Sobi, participated on advisory boards for Pfizer and received fees for participation in an educational meeting by UCB. D.W. has received financial support for an independent PhD studentship from GlaxoSmithKline and Alere and acted as a consultant for Roche Diagnostics. M.N. has received unit and individual support to attend meetings from UCB and Jansen UK and participated on an expert panel for UCB. M.K. has received individual support to attend meetings from GlaxoSmithKline, UCB and Astra-Zeneca, chairing fees from Bristol-Myers Squibb and honoraria from GlaxoSmithKline/Human Genome Sciences, Medimmune, INOVA Diagnostics and Merck. M.G. has received individual support to attend a meeting from Roche. All others have declared no conflicts of interest.

Supplementary data

The full guideline is available as supplementary data at *Rheumatology* Online.

References

1 Østensen M, Andreoli L2, Brucato A *et al*. State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev 2015;14:376–86.

2 Østensen M, Khamashta M, Lockshin M *et al*. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006;8:209.

3 Østensen M, Lockshin M, Doria A *et al*. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. Rheumatology 2008;47:iii28–31.

4 Flint J, Panchal S, Hurrell A *et al*. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice. Rheumatology 2016;55:1698–1702.