Brighton and Sussex University Hospitals NHS Trust

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Guideline for the Treatment of Autoimmune Inflammatory Rheumatic Diseases with High Cost Drugs (HCDs)

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Version 1.0

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Version control

Revision history

Revision Date	Actioned by	Summary of Changes	Version
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Contents

Introduction

The aim of this document is to provide guidance around treatment decisions for biologic and targeted synthetic DMARDs (tsDMARDs) to treat adult patients with autoimmune inflammatory rheumatic diseases. The guidance has been written based on up to date evidence and published research, however it also reflects locally adopted practice at BSUH NHS Trust.

Guidelines should be tailored where necessary to individual patient needs. They do not replace the need for consultation with senior staff and/or referral for expert advice.

NICE Guidance

Links for the relevant NICE guidance are given below. As new high cost drugs are approved they will be considered for inclusion in the treatment pathway (appendix 2-to be added) based on NICE recommendations and approval by the local Area Prescribing Committee.

Rheumatoid Arthritis

Technology appraisal guidance [TA375] Published date: 26 January 2016 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.

Technology appraisal guidance [TA195] Published date: 25 August 2010 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Technology appraisal guidance [TA225] Published date: 22 June 2011 Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

Technology appraisal guidance [TA247] Published date: 22 February 2012 Tocilizumab for the treatment of rheumatoid arthritis

Technology appraisal guidance [TA485] Published date: 01 November 2017 Sarilumab for moderate to severe rheumatoid arthritis

Technology appraisal guidance [TA466] Published date: 09 August 2017 Baricitinib for moderate to severe rheumatoid arthritis

Juvenile Idiopathic Arthritis (JIA)

Technology appraisal guidance [TA373] Published date: 16 December 2015 Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis

Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA). Reference: NHS England E03X04. Publication date July 2015.

Ankylosing Spondyloarthritis and Psoriatic arthritis

Technology appraisal guidance [TA407] Published date: 28 September 2016Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Golimumab for treating non-radiographic axial spondyloarthritis

Technology appraisal guidance [TA497] Published date: 10 January 2018

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

Technology appraisal guidance [TA199] Published date: 25 August 2010

Technology appraisal guidance [TA340] Published date: 04 June 2015 Last updated: 03 March 2017 Ustekinumab for treating active psoriatic arthritis

Technology appraisal guidance [TA445] Published date: 24 May 2017 Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs

Technology appraisal guidance [TA433] Published date: 22 February 2017 Apremilast for treating active psoriatic arthritis

Technology appraisal guidance [TA543] Published date: 03 October 2018 Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs

Technology appraisal guidance [TA537] Published date: 08 August 2018 Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs

Other

Technology appraisal guidance [TA518] Published date: 18 April 2018 Tocilizumab for treating giant cell arteritis

Technology appraisal guidance [TA397] Published date: 22 June 2016 Belimumab for treating active autoantibody-positive systemic lupus erythematosus

Biosimilars

A biosimilar medicine is a biological medicine manufactured to be highly similar to an existing licensed "reference" biological medicine, with no meaningful differences from the reference medicine in terms of quality, safety or efficacy. In 2017 The British Society for Rheumatology (BSR) published a position statement regarding biosimilars[1.] The principals of this statement should be followed when prescribing for conditions covered by this guidance, for example:

- Prescribe by brand name
- Substitution only with the consent of the prescribing clinician (not at the point of dispensing).
- Decisions regarding switching should made in partnership with the patients

Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of the originator.

Pre biologic Screening

Please refer to appendix 1

Peri-operative management of biologics

Prevention of the risk of potential infection by stopping a patient's biologic agent prior to surgery should be weighed alongside the risk of a flare and additionally the increased risk of infection should steroid treatment be required to treat any flare (even at low doses). Rheumatoid Arthritis (RA) flares develop in 10-20% of patients undergoing surgery and have a potential to impact adversely on post-operative recovery, in addition active RA increases infection risk.[2]

BSR guidelines recommend for most biologics (exceptions: rituximab and tocilizumab), consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug.[3] For high risk procedures (e.g. bowel surgery) consideration should be given stopping 3-5 half-lives (if this is longer than one dosing interval) before surgery.

For patients receiving rituximab treatment should ideally be stopped 3-6 months prior to elective surgery. For patients receiving tocilizumab IV stop at least 4 weeks before surgery; for SC tocilizumab stop at least 2 weeks before surgery.

Table One: Time to stop biologic prior to surgery

Biologic agent	Dosing frequency	Half-life (days)	Time to stop prior to surgery
Abatacept	Weekly	14	2 weeks
Adalimumab	Every 2 weeks	14	2 weeks
Anakinra*	Daily	6 (hours)	1 week
Apremilast	Twice daily	9 hours	1 week
Baricitinib	Daily	12.5 (hours)	1 week
Certolizumab	Every 2 weeks	14	2 weeks
Etanercept	Weekly	3	1 week
Golimumab	Monthly	14	4 weeks
Infliximab	8 weekly	9	4,6 or 8 weeks
Ixekizumab	Every 4 weeks	13	4 weeks
Rituximab	Variable (max 6 monthly)	21 days	3-6 months**
Sarilumab	Every 2 weeks	21	2 weeks
Secukinumab	Monthly	27	4 weeks
Tocilizumab IV	4 weekly	13	4 weeks
Tocilizumab SC	Weekly	13	2 weeks
Tofacitinib	Twice daily	3 (hours)	1 week
Ustekinumab	Every 12 weeks	21	12 weeks

*Note anakinra is not NICE approved for RA

** Discuss with rheumatology

In practice the surgical team should ideally liaise with the patient's rheumatologist to discuss the plan for the patients' treatment around the planned procedure.
Biologics may be recommenced after surgery when there is good wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection.

Infections advice for patients

If unwell with a temperature or taking antibiotics patients are advised to miss the biologic / ts DMARDs and restart when well and any antibiotics have finished.

Family Planning, Pregnancy and Breast Feeding

The prescribing of many drugs in pregnancy is complicated by a lack of knowledge regarding their compatibility, thus 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 and there is growing evidence of drug safety in pregnancy. The BSR published guidance on prescribing drugs in pregnancy and breastfeeding in 2016[4] however treatment decisions should be individualised, taking into account alternative therapies, risk of flare and the impact of this on the mother and unborn child. Some recommendations will be off label for the products and this must be discussed with the patient. Where there is no data available discuss with rheumatology or pharmacy.

Table Two: Compatibility with Pregnancy, Breast feeding and Paternal Exposure

Medication	Compatible peri-conception	Compatible with first trimester*	Compatible with second/third trimester*	Compatible with breast feeding	Compatible with paternal exposure
Apremilast	No	No	No	No data	No data
Abatacept	No	No[1]	No	No data[4]	No data[3]
Adalimumab	Yes	Yes	Second but not third	Yes	Yes
Anakinra	No data	No[1]	No	No data[4]	No data[3]
Baricitinib	Stop 1 month in advance	No	No	No data	No data
Certolizumab	Yes	Yes	Yes	Yes	Limited data[2]
Etanercept	Yes	Yes	Second but not third	Yes	Yes
Golimumab	No data	No data	No data	No data	No data
Infliximab	Yes	Yes	Stop at 16 weeks	Yes	Yes
Ixekizumab	No data	No	No	No data	No data
Rituximab	Stop 6 months in advance	No[1]	No	No data[4]	Yes
Sarilumab	No data	No	No	No data[4]	No data
Secukinumab	No data	No	No	No data	No data
Tocilizumab SC	Stop 3 months in advance	No[1]	No	No data[4]	No data[3]
Tofacitinib	Stop 1 month in advance	No	No	No data	No data

Ustekinumab	No data	No	No	No data[4]	No data

Notes:

*The first trimester is generally considered to be from week 0-13 and the second from week 14 to week 26, the third from week 27-40.

[1]Unintentioinal first trimester exposure is unlikely to be harmful

[2]Data from the SmPC indicates there is unlikely to be an issue

[3]Unlikley to be harmful

[4] If required by the mother, it is not a reason to discontinue breastfeeding. Until more data become availableuse with caution during breastfeeding, especially while nursing a newborn or preterm infant[8]

Breast feeding

In many cases there is insufficient information on the excretion of medications into human breast milk and the likely effects of this in the infant. Theoretically large protein molecules are likely to be transferred to breast milk in very small amounts and to be destroyed by the infant's gastrointestinal tract, even if they were present in breast milk. However the use in breast feeding is contraindicated by most manufacturers and is therefore off label. A decision as to whether to breastfeed should be made on an individual basis weighing the benefits of feeding to the child and of the medication to the woman.

Vaccination of infants

If biologics are continued later into pregnancy than the second trimester to treat active disease, then live vaccines should be avoided in the infant. The following hyperlink is for the current vaccine schedule for infants in the UK. This is frequently updated (hence recommendations not reproduced within document). 'Complete Routine Immunisation Schedule: Immunisation information for health professionals and immunisation practitioners'. Public Health England. https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule

The only infant live vaccines routinely scheduled at time this document was ratified (January 2020) is Rotavirus at 8 and 12 weeks. Additionally the BCG vaccine may be recommended in special groups as below.

- Infants in areas of the country with TB incidence >= 40/100,000
- Infants with a parent or grandparent born in a high incidence country (Where the annual incidence of TB is >= 40/100,000) See www.gov.uk/government/publications/tuberculosis-tb-by-country-rates-per-100000-people

The period before which live vaccines may be given is the subject of some debate. The BSR guidelines[4] state wait until the infant is 7 months old, the recently published EULAR vaccination recommendations[6] state 6 months as does the Green Book[7], however the summary of product characteristics for the individual medicines sometimes gives a shorter interval. Where this is the case this is documented in table 4 below. Additionally the time quoted by the manufacturer is usually the time since the last dose rather than since birth.

It is worthy of note that as many women discontinue therapy in the third trimester a period of three months may have already elapsed at birth since last exposure.

Table Four: Recommended time since biologic before administration of live vaccines (if product is not listed no recommendation is made in the SmPC)

Medication	Time before live vaccination (since mothers last dose)
Abatacept	14 weeks
Adalimumab (Humira/Imraldi/Amgevita)	5 months
Certolizumab	5 months
Etanercept (Benepali/ Enbrel)	16 weeks
Golimumab	6 months
Infliximab	6 months (from birth)*

*As per SmPC

- **Rotavirus vaccine**

The first dose of Rotavirus vaccine may be delayed up to an age of 14 weeks and 6 days, the second dose given after a period of 4 weeks and by 23 weeks and 6 days of age. The age limit is to minimise a potential risk of intussusception.

The green book states there are very few infants who cannot receive the rotavirus vaccine (with the exception of severe combined immune-deficiency) and that the benefit from vaccination may exceed any risk in other forms of immunosuppression.[7]

BCG Vaccine

Some cases of fatal BCG infection in infants after in utero exposure to TNF alpha antagonists have been reported through the Yellow Card scheme. Immunisation with BCG, should be delayed for 6 months in children born of mothers who were on immunosuppressive biological therapy during pregnancy.[7]

Vaccination advice for patients on biologics and targeted synthetic DMARDs

During biologic therapy influenza vaccine is recommended annually and pneumococcal vaccination five yearly. The recommendation for five yearly pneumococcal vaccination is based on the evidence that protection has been shown to wane after a period of five years and repeat vaccination is recommended in conditions with a similar level of immunosuppression.[7]

The administration of live vaccines is not recommended in patients on biologic or tsDMARDs. As live vaccines replicate after administration, individuals who have received a live vaccine should wait until their immune response has been established to receive immunosuppressive therapy. For most viral live vaccines a period of up to four weeks should be a sufficient.

Should a patient who is already initiated on therapy require a live vaccine, a washout period based on the half-life of the drug should be considered (see table one), 4-5 half-lives is sufficient for total elimination, although the clinical effect of the drug may persist beyond this time period e.g. rituximab.

Table 5 shows live vaccines available in the UK

Table Five: UK Live vaccines

Live vaccine	Brand name
BCG	Baccillus Calmette-Guerin Vaccine
Influenza (nasal)	Fluenz, Tetra
Measles, Mumps and Rubella combined vaccines (MMR)	MMRvaxPRO®, Priorix®
Poliomyelitis (Live oral vaccine)	Poliomyeltis Vaccine, live (oral) GSK OPV
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster Vaccines	Varilrix®, Varivax®, Zostavax®
Yellow Fever	Stamaril®

Household contacts and live vaccines

Most live vaccines can be safely given to close contacts of immunosuppressed individuals as transmission to contacts does not occur or can be minimised by simple precautions (e.g. careful hand washing) In addition, vaccination of close contacts of vulnerable people has a major benefit by reducing the risk of exposure to wild-type infection. This advice includes the MMR, Rotavirus, live influenza and shingles vaccines. Contacts of immunosuppressed individuals who develop a vesicular rash after receiving live varicella or shingles vaccine should attempt to restrict exposure of the vulnerable person (for example by covering a localised rash, or by avoiding face to face contact) until the rash is dry and crusted.

The latest EULAR guidance[6] recommends that highly immunocompromised individuals avoid contact with the nappies of infant's for four weeks following vaccination against rota virus. This may be highly impractical and where it is not possible careful hand washing should be adopted.

Dog owners should be warned that the kennel cough vaccine (Bordetella bronchiseptica) is live and it is possible for the infection to pass from dog to human[8.] If intranasal vaccination with modified live kennel cough vaccine is used, immunocompromised owners should not be in the same room during vaccination. They should avoid contact with the dog's mouth, nose and face for at least a few days after vaccination and should wash their hands regularly after contact with the dog. If respiratory disease develops in someone exposed to a dog recently vaccinated against kennel cough, the potential for vaccine-associated disease should be mentioned to the treating clinician.

Inactivated vaccines

Inactivated vaccines are considered safe to administer to people on immunosuppressant and biologic therapies. Pneumococcal vaccine should ideally be given 2-4 weeks before commencing therapy and response may be reduced if administered after commencing. For attenuated vaccines generally the advice is that immunosuppressive treatment should not be delayed if this could result in worsening of the underlying condition[7].

Storage of biologic medicines

Most biologics require refrigerated storage; however there is data to support the use of single devices after they have been kept at room temperature for a limited time. The table below summarises this data. In individual cases of temperature excursion always contact the company as further data may be available based on individual circumstances.

Table Six: Time biologic medicines can be out of the fridge[11]

Medication	Storage at Room Temperature
Amgevita	2 weeks*
Benepali	4 weeks*
Cimzia (Certolizumab)	10 days*
Cosentyx (Secukinumab)	4 days*
Enbrel	4 weeks*
Humira	2 weeks*
Imraldi	4 weeks*
Kevzara (Sarilumab)	14 days*
Kineret (Anakinra)	12 hours*
Orencia (Abatacept)	8 Hours*
RoActemra (Tocilizumab)	8 Hours*
Simponi (Golimumab)	30 days*
Stelara (Ustekinumab)	4 hours**
Talz (Ixekizumab)	5 days*

*Drug must then be used or disposed of, do not return to fridge

**Can then be returned to the fridge

Metoject can be stored at room temperature, between 2-25 degrees. The manufacturer advises if the temperature is likely to exceed 25 degrees that the product is stored in the fridge.[12]

References

1. British Society for Rheumatology January 2017 Position statement: Biosimilar medicines https://www.rheumatology.org.uk/Portals/0/Documents/Policy/Position%20statements/Biosimilars.pdf?ver=2019-02-27-170506-670

2. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs
Jo Ledingham et al; Rheumatology 2017;56:865_868
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3. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis
Christopher R. Holroyd et al; Rheumatology 2019;58:e3_e42
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4. 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 et al; Rheumatology 2016;55:1693-1697
https://academic.oup.com/rheumatology/article/55/9/1693/1744535

5. The complete routine immunisation schedule
https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule

6. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases
Victoria Fureret al;
https://ard.bmj.com/content/annrheumdis/early/2019/09/18/annrheumdis-2019-215882.full.pdf

7. The Green Book-Immunisation against infectious diseases
https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

8. Bordetella bronchiseptica pneumonia in a kidney-pancreas transplant patient after exposure to recently vaccinated dogs
Gisel JJ[1], Brumble LM, Johnson MM Transpl Infect Dis. 2010 Feb;12(1):73-6. doi: 10.1111/j.1399-3062.2009.00451.x. Epub 2009 Oct 28

9. Gotestam Skorpen C, Hoeltzenbein M, Tincani A et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795-810. PMID: 26888948

10. Lactmed Database
https://www.toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~Jwz4X9:1

11. EMC website for individual products and data on file
https://www.medicines.org.uk/emc/

12. Data on File Medac GmBH 29/11/2019

Appendix one: Suggested checklist for patient screening

Screening investigations to be requested in clinic			
FBC/U&Es/LFTs/ESR/CRP (within last 6 weeks)			
HIV/HBSag/HBSab/HBcag/HCV			
Varicella Zoster IgG if Hx uncertain			
Chest X-Ray (within the last 12 months)			
T-spot (within12 months)			
Rituximab			
Serum Immunoglobulins (document and monitor low IgG)			
Tocilizumab			
Lipid profile at baseline and 4-8 weeks after initiation			
Enhanced LFT monitoring (every 4-8 weeks for first 6 months the 12 weekly)			
JAK inhibitors			
Lipids baseline and 8 weeks after initiation for tofacitinib and 12 weeks after initiation for baricitinib			
VZV Hx			
DVT risk assessment			
Screening questions to be asked in clinic			
Hx of Heart Failure			
Hx MS			
Hx Cancer			
Hx Breathing problems			
Hx of recurrent infections			
Hx TB			
Tocilizumab (caution re perforation risk)			
Advice to be given in clinic			
Vaccination advice			
Infections advice			
Family planning and breast feeding advice (if appropriate)			
Travel advice			
Counselled and educated			
Patient alert card given			
Consent for homecare			
Contact details for department			
Scores recorded for funding			