PROTOCOL FOR

Prescription and follow up of biologics and targeted Synthetic Disease Modifying Anti-Rheumatic Drugs (b/tsDMARDS) in the management of Chronic Inflammatory Rheumatic Diseases (CIRDs):

- ✓ *Rheumatoid Arthritis RA*
- ✓ *Axial SpondyloArthritis AxSpa*
- ✓ *Psoriatic Arthritis PsA*

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1. Target population and diseases definition:

The target population comprises patients with the following diseases as diagnosed by a rheumatologist registered at the MOH:

1- Rheumatoid Arthritis RA (M06.9)
2- Axial SpondyloArthritis:
    a. Ankylosing spondylitis AS (M45)
    b. Non-radiographic axial spondyloarthritis Nr-axSpA (M45)
3- Psoriatic Arthritis PsA (L40.5)

Elements used for diagnosis and follow up should be mentioned in the application form to be filled by the treating Rheumatologist

2. Pre-treatment work-up:

Before initiating a biologic/ Ts DMARDs treatment, Patients should have mandatory screening with:

- CBC, ESR or CRP, creatinine, ASAT,ALAT
- HBs antigen, HBc antibodies, HCV antibodies
- PPD or Quantiferon/ IGRA
- Chest X-ray

Special Population:

- Depending on the patient's risk factors and family history, other screening tests may be ordered: HIV antibodies, mammogram, chest CT-scan,…
- A patient with positive PPD needs to do a Quantiferon/IGRA test and obtain a clearance from an infectious diseases specialist before starting a biologic treatment

3. Pre-treatment Vaccination:

All patients must receive anti-pneumococcal vaccine and, when available, flu vaccine before starting the bDMARDs and tsDMARDs therapy, unless justified otherwise by the rheumatologist.

Special Population:

Depending on the patient's risk factors and rheumatologist's opinion, the patient may be eligible for other vaccines prior to the initiation of the bDMARD

4. Lebanese MOH protocol for the prescription and follow up of Biologics and targeted Synthetic Disease Modifying Anti-Rheumatic Drugs in Rheumatoid Arthritis

a) Indications of bDMARDs or tsDMARDs in RA:

To be eligible for a bDMARD or a tsDMARDs, patients diagnosed with RA should fulfill all the following conditions:

1. Failure of at least one **csDMARDs** (methotrexate, Leflunomide or sulfasalazine) taken at maximal tolerated dose for **at least 3 months**. In case the response was not satisfactory within 3 months consider combination of **2 csDMARDs** before moving to the **advanced therapy** if prognostically unfavorable factors are absent (RF/ACPA, High disease activity).
2. Active disease according to a composite measure including clinical and non-clinical parameters (DAS28 of more than 3.2)
3. Active disease according to rheumatologist's opinion

b) bDMARDs and tsDMARDs treatment algorithm in RA:

i. Available bDMARDs at MOH:

- Anti-TNF alpha monoclonal antibodies
  - Adalimumab (Humira® 40 mg)
  - Certolizumab pegol (Cimzia® 200mg)
  - Golimumab (Simponi® 50 mg)
  - Infliximab (Remicade® 100mg)
- Anti-TNF alpha receptor antagonist:
  - Etanercept (Enbrel® 50mg)
- Anti-IL6
  - Tocilizumab (Actemra® 400 mg , 200 mg and 80 mg IV and Actemra® 162 mg SQ)
- Anti- CTLA-4
  - Abatecpt (Orencia® 250 mg IV and Orencia® 125 mg SQ)
- Anti CD20
  - Rituximab (Mabthera® 500mg IV)

ii. Available tsDMARDs at MOH:

- Janus Kinase inhibitor (JAKi)
  - Tofacitinib (Xeljanz® 5mg)

iii. Choice of the bDMARDs :

The choice of prescription of a first line bDMARDs or tsDMARDs depends on the following:

- **Shared decision** between the patient and the rheumatologist with regards to previous history, extra-articular manifestations, comorbidities , contraindications and potential adherence to treatment (Patient Preference)
- **Availability of the DMARDs at the MOH**: knowing that all the above medications can be used as first line treatment except for rituximab which should be kept for second line treatment (Rituximab may be used as first line biologic treatment in certain conditions, such as recent history of malignancy or current malignancy)

Special populations:

- **Monotherapy**: in case of csDMARDS are inappropriate or in case of intolerance to several csDMARDs, molecules preferred in monotherapy modality are Tocilizumab and Tofacitinib. In other cases, it is preferable to use bDMARDs and ts DMARDs in association with csDMARDS (*Infliximab and Golimumab should be always used in combination)*
- **Frequent Serious infections**:
  tsDMARDs may be considered before bDMARDs
- **Pregnancy:** Among bDMARDs, continuation of tumor necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. *Etanercept and certolizumab* may be considered for use throughout pregnancy due to low rate of transplacental passage. There is currently not enough data for using other molecules in pregnancy
- **Renal, hepatic, pulmonary and cardiac failure patients** should be managed in collaboration with the respective discipline.

5. Lebanese MOH protocol for the prescription and follow up of Biologic Disease Modifying Anti-Rheumatic Drugs in Axial SpondyloArthritis

a) Indications of bDMARDs in axSpA:

To be eligible for a bDMARD therapy, patients diagnosed with axSpA should fulfill all of the following four conditions:

i. Active disease according to ASDAS(≥2.1) or BASDAI (≥4)
ii. Active disease as per the rheumatologist opinion
iii. Elevated CRP and/or positive MRI and/or Radiographic sacroiliitis (Radiographic Sacroiliitis is mandatory before initiating Infliximab and IL17 treatment since both medications are not approved in nr-axSpA)
iv. Failure or intolerance of at least two NSAIDs, taken each for 2 to 4 weeks at the maximum tolerated dose.

Exception to iv condition: Patients with contra indications to NSAIDs i.e. *inflammatory bowel diseases, renal failure or any other condition* justified by the rheumatologist

b) bDMARDs treatment algorithm in axSpA:

i. Available bDMARDs at MOH:

- Anti-TNF alpha monoclonal antibodies
  - Adalimumab (Humira® 40 mg)
  - Certolizumab pegol (Cimzia® 200mg)
  - Golimumab (Simponi® 50 mg and 100 mg)
  - Infliximab (Remicade® 100mg)
- Anti-TNF alpha receptor antagonist:
  - Etanercept (Enbrel® 50mg)
- Anti-IL17A
  - Secukinumab (Cosentyx® 150 mg)

ii. Choice of the bDMARDs:

The choice of prescription for a first line bDMARDs depends on the following:

- Shared decision between the patient and the rheumatologist with regards to previous history, extra-articular manifestations, comorbidities , contraindications and potential adherence to treatment (patient preference)
- Availability of the DMARDs at the MOH
- Current practice (first bDMARDs) is to start with Anti-TNF therapy**.**
- if Anti-TNF therapy fails, switching to another Anti-TNF or Anti IL17 therapy should be considered

Special Population:

- **IBD:** Anti TNF alpha monoclonal antibodies are recommended over other bDMARDs (Certolizumab in CD only and Golimumab in UC only)
- **Uveitis:** Adalimumab and Infliximab are recommended over other bDMARs
- **Pregnancy**: Among bDMARDs, continuation of tumor necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. *Etanercept and certolizumab* may be considered for use throughout pregnancy due to low rate of transplacental passage. There is currently not enough data for using anti- IL17 in pregnancy
- **Renal, hepatic, pulmonary and cardiac failure patients** should be managed in collaboration with the respective discipline.

6. Lebanese MOH protocol for the prescription and follow up of Biologic and targeted Synthetic Disease Modifying Anti-Rheumatic Drugs in Psoriatic Arthritis

a) Indications of bDMARDs or tsDMARDs in PsA:

To be eligible for a bDMARD or a tsDMARDs, patients diagnosed with PsA should fulfill all the following conditions:

1. Failure or intolerance to NSAIDs
2. Failure of at least one csDMARDs (i.e. methotrexate at maximal dose) taken for at least 3 months
3. Active disease according to rheumatologist's opinion
4. Active disease according to one preferred composite measure (DAPSA>28)

- Exception to condition 1: Patients with contra-indications to NSAIDs i.e. *inflammatory bowel diseases, renal failure or any other condition* justified by the rheumatologist can skip this condition
- Exception to condition 2: Patients with severe axial manifestations or severe enthesitis can skip this condition

b) bDMARDs and tsDMARDs treatment algorithm in PsA:

i. Available bDMARDs at MOH:

- Anti-TNF alpha monoclonal antibodies
  - Adalimumab (Humira® 40 mg)
  - Certolizumab pegol (Cimzia® 200mg)
  - Golimumab (Simponi® 50 mg and 100 mg)
  - Infliximab (Remicade® 100mg)
- Anti-TNF alpha receptor antagonist:
  - Etanercept (Enbrel® 50mg)
- Anti-IL17A
  - Secukinumab (Cosentyx® 150 mg)
- Anti-IL 12/23
  - Ustekinumab (Stelara® 45 mg and 90mg)
- Anti CTLA-4
  - Abatacept (Orencia® 250 mg IV and Orencia® 125 mg SQ)

ii. Available tsDMARDs at MOH:

- Janus Kinase inhibitor (JAKi)
  - Tofacitinib (Xeljanz® 5mg)
- Phosphodiesterase 4 inhibitor (PDE4i)

- Apremilast (Otezla® 30mg)

iii. Choice of the DMARDs:

The choice of prescription for a first line bDMARDs or tsDMARDs depends on the following:

- Shared decision between the patient and the rheumatologist with regards to previous history, extra-articular manifestations, comorbidities , contraindications and potential adherence to treatment (patient preference)
- Availability of the DMARDs at the MOH
- Current practice (first bDMARDs) is to start with Anti-TNF therapy
- If Anti-TNF therapy fails, switching to *another Anti-TNF or Anti IL17 or Anti IL12/23 or abatacept* therapy should be considered
- In case of bDMARDs fail or are inappropriate, *tsDMARDs such as phosphodiesterase 4 inhibitor (Apremilast) or JAK- inhibitor (Tofacitinib)* may be used

Special Population:

- **Predominant Axial spondyloArthritis:**
  - bDMARDs (Anti TNF as first choice) can be considered even if no csDMARDs have been tried, since csDMARDs have no proven efficacy in axial disease
  - In case of Anti TNF therapy fail or is inappropriate, IL17 inhibitors should be considered
  - Data is limited on the efficacy of IL12/23 and tsDMARDs
- **Predominant Enthesits/ Dactylitis**
  - bDMARDs can be considered even if no csDMARDs have been tried, since csDMARDs have no proven efficacy in treating these aspects of PsA especially enthesitis. A local corticosteroid injection should be considered before bDMRARDs
- **IBD**
  - Anti TNF alpha monoclonal antibodies are recommended over other bDMARDs *(Certolizumab in CD and Golimumab in UC only*)
  - In case of Anti TNf therapy fail or are inappropriate, ustekinumab is recommended
- **Uveitis:** Adalimumab and Infliximab are recommended over other bDMARDs
- **Frequent serious infections:**
  - tsDMARDs are preferred over bDMARDs
  - IL12/23 inhibitor or IL17 Inhibitor are preferred over Anti TNF
- **Pregnancy**: Among bDMARDs, continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered.

Etanercept and Certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage. There is currently not enough data for using anti- IL17 and anti-IL12/23 in pregnancy

- **Renal, hepatic, pulmonary and cardiac failure patients** should be managed in collaboration with the respective discipline.

7. Requirement for Biologics/tsDMARDs treatment renewal for the management of CIRDs:

To be eligible for bDMARD or tsDMARD therapy renewal, patients should fulfill the following two conditions:

- Evidence of an adequate treatment response as per composite outcome measure related to each disease
    - RA: DAS28 improvement of 1.2 points or more
    - AS and nr-axSpA: ASDAS (> 1.1 improvement) or BASDAI (> 50% improvement or 2 points)
    - PsA: DAPSA score or >50% decrease in inflammatory markers (CRP)
- Absence of side effects and/or toxicity with a blood test within normal range (CBC , creatinine, ASAT, ALAT)

Exceptions can be considered in the presence of other external conditions interfering with inflammatory markers, according to physician's judgement

- Intervals for renewal: File renewal should occur every 6 months

8. Requirement for treatment switching:

To be eligible for switching between DMARDs , patients should fulfill the following two conditions:

- Evidence of treatment non response or loss of response
    - RA: DAS 28 improvement below 1.2
    - AS and nr-axSpA: ASDAS (<1.1 improvement) or BASDAI (< 50% improvement or 2 points)
    - PsA: DAPSA or <50% decrease in inflammatory markers (CRP)
- Adequate wash out period between the 2 bDMARDs

- Intervals for switching: 12 weeks at least in case of non-response or loss of response. The interval may be shorter in case of premature treatment discontinuation due to side effects

Remarks:

- **Active Switching** between bDMARDs without any medical reason is not permitted.
- **Active Switching** between originator and biosimilar DMARDs without the rheumatologist's approval is not permitted

9. Treatment tapering

If patient is in a sustained remission (12 months), tapering down of the DMARD can be considered

10.Protocol review

Internal review:

Internal review of this protocol should be repeated on a yearly basis by a committee appointed by the MOH. Review may occur exceptionally earlier in case of a major scientific breakthrough

External review:

An External review by an international expert should be done at the initiation of this protocol and at later stages if required by the internal review committee.

11.Protocol dissemination:

This Protocol will be published on the MOH official website and will be communicated to the scientific committee of the Lebanese order of Physicians LOP and the Lebanese Society of Rheumatology (LSR)

Abbreviations

MOH	Ministry Of Health
RA	Rheumatoid Arthritis
axSpA	Axial SpondyloArthritis
AS	Ankylosing spondylitis
nr-axSpA	Non Radiographic Axial Spondyloarthritis
PsA	Psoriatic Arthritis
IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
csDMARDs	Conventional synthetic Disease-Modifying AntiRheumatic Drugs
bDMARD	biologic Disease-Modifying AntiRheumatic Drugs
tsDMARD	Targeted synthetic Disease-Modifying AntiRheumatic Drugs
TNF	Tumor Necrosis Factor
IL	Interleukin
JAK	Janus Kinase
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ASAS	Assessment of SpondyloArthritis international Society
MRI	Magnetic Resonance Imaging
DAS	Disease Activity Score
ASDAS	Ankylosing Spondylitis Disease Activity Score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
DAPSA	Disease Activity in Psoriatic Arthritis
ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein

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