ABSTRACT

Objective: To update the recommendations for the treatment of rheumatoid arthritis (RA) with biological therapies, endorsed by the Portuguese Society of Rheumatology (SPR).

Methods: These treatment recommendations were formulated by Portuguese rheumatologists based on literature evidence and consensus opinion. At a national meeting the 11 recommendations were discussed and updated. The document resulting from this meeting circulated to all Portuguese rheumatologists, who anonymously voted online on the level of agreement with the recommendations.

Results: These recommendations cover general aspects as shared decision, prospective registry in Reumapt, assessment of activity and RA impact and treatment objective. Consensus was also achieved regarding specific aspects as initiation of biologic therapy, assessment of response, switching and definition of persistent remission.

Conclusion: These recommendations may be used for guidance of treatment with biological therapies in patients with RA. As more evidence becomes available and more therapies are licensed, these recommendations will be updated.

Keywords: Guidelines; Biologics; Rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, with an estimated prevalence of 0.7% in adult Portuguese population1.

The management of RA rests primarily on the use of disease-modifying anti-rheumatic drugs (DMARDs). These drugs reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage and thus interfere with the entire disease process. DMARDs include synthetic chemical compounds (csDMARDs) and biological agents (bDMARDs)2.

The appropriate use of anti-rheumatic drugs is critical and should be initiated as soon as possible, since its delay is associated with increasing joint damage and less drug-free remission3. The treatment objective should be to reach remission at the earliest possible
time point, based on a Treat-to-Target (T2T) strategy. T2T epitomizes the consensual concept that disease treatment should aim at achieving, as early as possible, and consistently maintaining a target level of disease activity. Clinical disease remission, or at least low disease activity, has become a possible and virtually mandatory target of treatment in recent treatment recommendations.

Biological therapies with different mechanisms of action are currently approved for RA. In Portugal, five original tumour necrosis factor inhibitors (TNFis) (infliximab, adalimumab, etanercept, golimumab and certolizumab pegol), one interleukin (IL)-6 receptor (IL-6R) blocking monoclonal antibody (tocilizumab), a T cell stimulation inhibitor (abatacept) and one B cell depleting agent (rituximab) are available. Currently biosimilar (bs) of infliximab and of etanercept (bs-infliximab, bs-etanercept) are also available. Other bs will soon enter the Portuguese market.

In 2003, the first version of the Portuguese Recommendations for the treatment of RA with biological therapy was developed by the Rheumatoid Arthritis Study Group (GEAR – Grupo de Estudos de Artrite Reumatóide) of the Portuguese Society of Rheumatology (SPR – Sociedade Portuguesa de Reumatologia) and published in Acta Reumatólogica Portuguesa. These guidelines have been regularly updated, as new evidence is published and the experience on their use increases, with the latest recommendations published in 2011. These recommendations are based on the standardized use of validated assessment tools of RA activity and impact: the disease activity score 28-joint count (DAS 28), the Health Assessment Questionnaire (HAQ) and the radiological assessment of Sharp score modified by van der Heijde (SvdH). A structured national registry of rheumatic patients, (Reuma.pt) incorporating disease assessment tools for RA has been created by the SPR and is available online.

This article presents the 2016 update of the Portuguese recommendations for the use of biological therapies in RA. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations.

These recommendations were formulated by Portuguese Rheumatologists based on literature evidence and consensus opinion. A draft of the recommendations and supporting evidence was first circulated to all Portuguese Rheumatologists. Secondly, at a national meeting, the recommendations were presented, discussed and revised. Finally, the document resulting from this meeting was again circulated to all Portuguese Rheumatologists, who anonymously voted online on the level of agreement with the recommendations. Agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).

These recommendations may be used for guidance in deciding which patients with RA should be treated with biological therapies. The use of biological therapies in RA is a rapidly evolving field and as more evidence becomes available and more therapies are licensed, these recommendations will be updated.

RECOMMENDATION 1

Rheumatologists are the specialists who should primarily care for RA patients.

Treatment of RA patients with bDMARDs must be based on a shared decision between patient and rheumatologist.

The rheumatologist is the specialist who should treat and monitor patients with RA. There is current evidence that patients with RA followed up by rheumatologists, in comparison with other doctors, are diagnosed earlier, receive DMARD treatment earlier and more frequently have better outcomes in all major characteristics of RA. Since patients with RA have high risk not only for disabilities related to their joint disease but also for comorbidities, such as infections, cardiovascular disease or malignancies, sometimes a multidisciplinary approach is required.

Sharing medical decisions is the foundation of the partnership between physicians and patients. It involves agreeing on the problem at hand, laying out the available options with their benefits and risks, eliciting the patient’s views and preferences on these options, and agreeing on a course of action. Shared decision making not only increases patient and physician satisfaction with healthcare, but also may improve health outcomes. This recommendation focuses on the need for information of the patient regarding the risks and benefits of the treatment. Due to the complexity, high cost, and potential toxicity of therapies for RA, patient information is central to safety and quality of care.

RECOMMENDATION 2

All RA patients receiving bDMARDs should be prospectively registered in the Reuma.pt.

Registries of patients with rheumatic diseases, especially under biological therapy, allow monitoring the efficacy and safety of the treatment. These registries have contributed to the increasing knowledge on the
performance of these drugs in real world. All instruments required to monitoring RA patients under biological therapy are available in Reuma.pt.\textsuperscript{15}

RECOMMENDATION 3
Monitoring RA patients under bDMARD is mandatory. These patients should be evaluated at closely spaced intervals, no longer than 3-4 months, to assess disease activity and safety issues. Function, quality of life and damage should be also evaluated during follow-up. Follow-up should be provided at closely spaced intervals (no longer than 3-4 months) in order to monitor the efficacy of bDMARDs and to identify potential side effects.

Tender and swollen joint counts, inflammatory markers [(erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], patient global assessment of disease activity (PGA) and physician global assessment (PhGA) should be collected at each evaluation. Patients should be evaluated using composite activity indexes (Table I). The most commonly used index is the DAS28 ESR, which has validated cut-offs for different activity levels\textsuperscript{12,25}. Other composite measures using joint counts, with validated cut-offs for disease activity, can be used, such as the Simplified Disease Activity Index (SDAI)\textsuperscript{26} or the Clinical Disease Activity Index (CDAI)\textsuperscript{27}. The DAS28 CRP has no validated cut-offs for remission or low disease activity. All these variables and indexes are available in Reuma.pt.

The global impact of the disease should also be evaluated. Functional impact using the HAQ, a validated tool available in Portuguese\textsuperscript{29}, should be performed at the beginning of bDMARDs and every six months. Physical Function not only provides information about the impact of RA but also predicts future outcomes. Quality of life (QoL) should also be periodically evaluated. Generic tools, as the Medical Outcome Study Short Form 36-item (MOS-SF36)\textsuperscript{28,30} and the EuroQol five dimensions questionnaire (EQ5D)\textsuperscript{31-33} are validated in Portuguese and available in Reuma.pt.

Structural disease progression should be evaluated, on radiographs of hands and feet, at the start of bDMARDs and latter repeated to support future treatment decisions.

RECOMMENDATION 4
The treatment target is remission or at least, low disease activity.

Besides clinical benefit, remission status has a significant impact on joint damage and deformities, physical function, QoL, comorbidities and mortality\textsuperscript{34,35}.

Remission is considered as the absence of symptoms and signs of inflammation. The several available disease activity indexes define differently “remission status” (Table I)\textsuperscript{25-27}. Observational studies have shown that remission does not mean the same in all these indexes, being the DAS28-ESR the least stringent criteria\textsuperscript{36-38}. In 2011, a collaborative research of American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) defined remission as tender joints, swollen joints, CRP and patient global assessment of disease activity all being ≤ 1\textsuperscript{39}. These new criteria are associated with less risk of radiographic progression and better outcomes\textsuperscript{40,41}. The proportion of patients reaching remission in clinical trials and clinical practice is sufficiently large to warrant its preferential use in clinical practice\textsuperscript{42}.

However, some studies have shown that many patients without clinical and laboratory findings of inflammation cannot be classified as being in remission due to the inclusion of PGA\textsuperscript{42}. It makes the ACR/EULAR remission difficult to apply in daily clinical practice, mainly in some clinical settings (eg. chronic pain syndrome, depression). In these difficult cases, more relevance can be given to the objective measures, like the inflammatory markers and swollen joints, since only those have been shown consistently to be associated

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Thresholds of disease activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS28-ESR</strong>\textsuperscript{25}</td>
<td>Remission ≤ 2.6</td>
</tr>
<tr>
<td></td>
<td>Low Activity ≥ 2.6 to &lt;3.2</td>
</tr>
<tr>
<td></td>
<td>Moderate Activity ≥ 3.2 to ≤ 5.1</td>
</tr>
<tr>
<td></td>
<td>High Activity &gt; 5.1</td>
</tr>
<tr>
<td><strong>SDAI</strong>\textsuperscript{26}</td>
<td>Remission ≤ 3.3</td>
</tr>
<tr>
<td></td>
<td>Low Activity &gt; 3.3 to ≤ 11</td>
</tr>
<tr>
<td></td>
<td>Moderate Activity &gt; 11 to ≤ 26</td>
</tr>
<tr>
<td></td>
<td>High Activity &gt; 26</td>
</tr>
<tr>
<td><strong>CDAI</strong>\textsuperscript{27}</td>
<td>Remission ≤ 2.8</td>
</tr>
<tr>
<td></td>
<td>Low Activity &gt; 2.8 to ≤ 10</td>
</tr>
<tr>
<td></td>
<td>Moderate Activity &gt; 10 to ≤ 22</td>
</tr>
<tr>
<td></td>
<td>High Activity &gt; 22</td>
</tr>
</tbody>
</table>

DAS28-ESR: 28-joint Disease Activity Score Erythrocyte Sedimentation Rate; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.
**Table II. Recommendations for the Use of Biological Therapies in Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Recommendation</th>
<th>Agreement Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Recommendation</td>
<td>Rheumatologists are the specialists who should primarily care for RA patients. Treatment of RA patients with biologic therapies (bDMARDs) must be based on a shared decision between patient and rheumatologist.</td>
<td>8.9 (2)</td>
</tr>
<tr>
<td></td>
<td>All RA patients receiving bDMARDs should be prospectively registered in the Rheumatic Diseases Portuguese Register (Reuma.pt).</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitoring RA patients under bDMARD therapy is mandatory. These patients should be evaluated at closely spaced intervals, no longer than 3 - 4 months, to assess disease activity and safety issues. Function, quality of life and damage should be also evaluated during follow-up.</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Treatment Target</td>
<td>The treatment target is remission or at least, low disease activity.</td>
<td>9.1 (1.3)</td>
</tr>
<tr>
<td>Treatment Indication</td>
<td>RA patients with inadequate response to methotrexate (MTX) at an optimal dose and for an adequate period of time, or to at least one other csDMARD in case of contraindication or intolerance to MTX, should be considered for bDMARD therapy.</td>
<td>9.3 (1.4)</td>
</tr>
<tr>
<td>First Line Treatment</td>
<td>Biological therapy should be started with any of the following drugs: TNF inhibitor (infliximab, etanercept, adalimumab, golimumab, certolizumab or approved biosimilars), tocilizumab or abatacept. Rituximab can be considered in some circumstances (see recommendation 7). bDMARDs should be administered in combination with MTX. If MTX is not tolerated or contraindicated, a bDMARD approved in monotherapy should be used.</td>
<td>8.9 (1.4)</td>
</tr>
<tr>
<td>Specific Comorbidities</td>
<td>Rituximab can be considered as first line biological treatment in case of patients with other conditions: hematologic neoplasms (B-cell-lymphomas, acute lymphoblastic leukaemia or monoclonal gammopathy of undetermined significance (MGUS)), latent tuberculosis in patients with contraindication to chemophrophylaxis, demyelinating diseases or specific manifestations of RA. The evidence to use rituximab in recent history of other neoplasms (and the required period) doesn't allow to state any recommendation, thus a decision should be made case by case.</td>
<td>8.8 (2)</td>
</tr>
<tr>
<td>Inadequate Response</td>
<td>Patients who failed a first bDMARD should be treated with another biological agent. If the first biological treatment was a TNF inhibitor, the patient may receive another TNF inhibitor or another biological agent with a different mode of action (tocilizumab, rituximab or abatacept). After two TNF inhibitor failures, switch to a biological agent with a different mode of action should be preferred. The choice of the following biological agent, should consider the reason for treatment discontinuation.</td>
<td>8.9 (1.3)</td>
</tr>
<tr>
<td>Sustained Remission</td>
<td>In case of sustained remission, tapering biological therapy can be considered especially in patients with concomitant csDMARDs treatment. No specific recommendations about tapering regimens can be made at the moment.</td>
<td>8.9 (1.5)</td>
</tr>
<tr>
<td>Pregnancy and Breastfeeding</td>
<td>Biological therapy should be avoided in pregnant and breastfeeding women. If pregnancy occurs, it is advisable to stop biological therapy,In some cases, based on shared decision between patient and physicians (rheumatologist and obstetrician), TNF inhibitor therapy can be considered in early stages of pregnancy. There is no indication to stop biological therapy in males who wish to become parents.</td>
<td>8.6 (1.8)</td>
</tr>
</tbody>
</table>

Agreement was voted on a scale 1 to 10 (fully disagreement to fully agreement) by 54 Rheumatologists.

RA, Rheumatoid Arthritis. bDMARDs, biologic disease-modifying anti-rheumatic Drugs. TNF, Tumor Necrosis Factor inhibitor. MGUS, monoclonal gammopathy undetermined significance. csDMARDs, conventional synthetic disease-modifying antirheumatic Drugs. HIV, human Immunodeficiency Virus. HCV, hepatitis C Virus. HBV, hepatitis B Virus. NYHA, New York heart.
with radiographic progression\textsuperscript{43}.

In some cases, like patients with long-standing or destructive disease, in whom remission is not achievable, low disease activity is acceptable\textsuperscript{2}.

**RECOMMENDATION 5**

RA patients with inadequate response to methotrexate (MTX) at an optimal dose and for an adequate period of time, or to at least one other csDMARD or in case of contraindication or intolerance to MTX, should be considered for bDMARD therapy.

MTX is the anchor treatment of RA patients, used in monotherapy or in combined therapy and should be part of the first line treatment of RA\textsuperscript{2}. In case of contraindication or intolerance to MTX, leflunomide and sulfasalazine should be started. Optimal dosage of MTX is 25-30 mg/week for at least 8 weeks. The optimal dosage of leflunomide is 20 mg/day and of sulfasalazine is 3-4 g/day, and may require longer period to achieve optimal benefit\textsuperscript{2}. All patients with no clinical improvement after 3 months, or who fail to achieve at least low disease activity (DAS <3.2) at 6 months after starting csDMARD therapy, should be considered as inadequate responders.

**RECOMMENDATION 6**

bDMARDs should be started with any of the following drugs: TNFi (infliximab, etanercept, adalimumab, golimumab, certolizumab or approved bs), tocilizumab or abatacept.

Rituximab can be considered in some circumstances (see recommendation 7).

bDMARDs should be administered in combination with MTX. If MTX is not tolerated or contraindicated, a bDMARD approved in monotherapy should be used.

Therapy with bDMARDs should be initiated with one of the following drugs authorized for first line use\textsuperscript{44}: TNFi (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol or approved bs), tocilizumab or abatacept.

In contrast to 2011 recommendations, anakinra is not considered for RA treatment since indirect comparisons with TNFi drugs showed a trend towards less efficacy for IL-1 inhibition\textsuperscript{45-47}.

All mentioned drugs have been proven to be effective in controlling disease activity, improving different patient reported outcomes (PROs) and slowing structural disease progression\textsuperscript{48-74}. Indirect comparison between the different bDMARDs\textsuperscript{47,75,76} and data from few head-to-head studies\textsuperscript{60,70,77} did not show statistically significant differences in efficacy and safety between them. Since no factors are available for guiding drug selection, no preference of one over another agent is recommended.

Rituximab combined with MTX has proven efficacy in treating RA after TNFi failure\textsuperscript{78-88} and is currently approved as second line therapy. Pivotal trials for Rituximab approval were done in TNF naïve patients and showed its efficacy in this context\textsuperscript{89}. Moreover, rituximab has also been studied in patients with active RA that have not been previously exposed to MTX. In the IMAGE trial, rituximab plus MTX was effective in reducing signs and symptoms of the disease as well as preventing radiographic damage in patients with early RA, MTX-naïve\textsuperscript{90}. Another study also showed improvement of physical function and quality of life in a similar population\textsuperscript{91}. However, rituximab is not licensed for use as a first-line biological agent therapy; it can be used under specific conditions (see recommendation 7).

There is no published evidence that TNFi, abatacept or rituximab alone are superior over MTX alone, whereas combination with at least 10mg/week of MTX, increases the efficacy and retention rate of biological treatment\textsuperscript{2,92-95}.

Etanercept, adalimumab, golimumab and certolizumab can be used in monotherapy if patients have intolerance or contraindication to MTX\textsuperscript{44}. This exception is based on some evidence suggesting that the drugs mentioned above may be effective in monotherapy, however study results have not been entirely coherent\textsuperscript{50,96-101}.

Tocilizumab is the only biological therapy that has demonstrated consistent evidence of its efficacy in monotherapy both for symptomatic control and inhibition of radiographic progression throughout several studies\textsuperscript{77,102-108}.

If MTX is not tolerated or contraindicated, a bDMARD approved in monotherapy\textsuperscript{44} should be used, with preference to tocilizumab.

With respect to bsDMARDs, the SPR position has been discussed in a separated article\textsuperscript{109}.

**RECOMMENDATION 7**

Rituximab can be considered as first line biological treatment in case of patients with other conditions: hematologic neoplasms [B-cell-lymphomas, acute lymphoblastic
leukaemia or monoclonal gammopathy of undetermined significance (MGUS)), suspected latent tuberculosis in patients with contraindication to chemoprophylaxis, demyelinating diseases or specific manifestations of RA. The evidence of rituximab use in patients with recent solid neoplasms does not allow to state any recommendation, thus a decision should be made case by case.

Rituximab has been used in patients with RA, but the largest experience comes from its use in the treatment of some hematologic neoplasms like B-cell-lymphomas and acute lymphoblastic leukaemia. Based on this, it seems reasonable that in patients with active or recent history of these cancers, in association with active RA, where other biological treatments are contra-indicated, rituximab could be used.

There is no evidence to support the recommendation of rituximab use in case of recently cured neoplasms. However, the absence of an increased risk of cancer in patients treated with rituximab support that some rheumatologists prioritize rituximab in this setting. This measure should be carefully decided, based on individual risk benefit and involving the oncology team.

Cases of tuberculosis have not been identified in patients receiving rituximab. Although rituximab therapy remains contra-indicated in active tuberculosis, its use can be considered in patients with suspected latent tuberculosis or living in endemic regions of tuberculosis who have contra-indication for chemoprophylaxis. bDMARDs are contra-indicated in patients with demyelinating diseases. Nevertheless, rituximab has been successfully used in patients with optic neuropathy and in patients with other demyelinating diseases such as multiple sclerosis. In patients suffering of both diseases (RA and a demyelinating diseases) rituximab could be considered.

RECOMMENDATION 8
Patients who failed a first bDMARD should be treated with another biological agent. If the first biological treatment was a TNFi, the patient may receive another TNFi or another bDMARD with a different mode of action (tocilizumab, rituximab or abatacept).

After two TNFi failures, switch to a bDMARD with a different mode of action should be preferred. The choice of the following bDMARDs, should consider the reason for treatment discontinuation. The treatment goal of remission should be assessed at 6 months. However, at 3 months after the start of biological therapy it is expected a minimal clinical improvement (change in DAS >1.2 or change from high to moderate disease activity). If there is no clinical improvement at 3 months, it is unlikely that the treatment goal will be achieved even in one year and changes in treatment strategy should be performed. If there is any clinical improvement at 3 months, maximum benefit with achievement of treatment goal (remission) will not be seen before 6 months of therapy in the majority of patients. Non-improvement at 3 months, or failing to achieve remission, or at least low disease activity, at 6 months is considered treatment failure.

All biological agents proved to be efficacious in case of TNFi non-response in clinical trials and are approved for this indication. After failing a first TNFi agent, there is no clear evidence that one bDMARD provides better efficacy than the others. Most the evidence comes from observational studies and from a few head-to-head clinical trials. Different studies have shown efficacy of switching to a second TNFi. Data from clinical trials and registries have shown that switchers responded to a second TNFi with significant reduction in disease activity. The probability of response to a switch from a monoclonal antibody (mAb) (infliximab/adalimumab) to the soluble receptor (SR) (etanercept) may be greater than vice-versa etanercept a mAb according to some studies, but it is still controversial. The probability of response to a second TNFi may be greater when the first TNFi is stopped due to other reason than primary failure.

After failing a TNFi, patients may be also given a non-TNFi agent, such as rituximab, tocilizumab or abatacept. Switching to rituximab proved to be beneficial. Several studies showed significantly greater clinical effectiveness compared to an alternative TNFi therapy after failing the first TNFi therapy, particularly in seropositive patients who switched due of inefficacy.

In the ARRIVE trial the switch from infliximab to abatacept proved to be safe and effective, with similar safety results between those that had a washout and those without a washout period after infliximab. Switching to tocilizumab is effective in achieving rapid and sustained improvements in signs and symptoms of RA.

Data from some observational studies have shown that patients with inadequate response to a TNFi who switched to a non-TNFi agent have significantly higher
drug retention rates, comparing to those that remain on TNFi treatment.\textsuperscript{118,120,131}

All bDMARDs have proved to be effective in patients failing a first TNFi agent. In the absence of a clear advantage of any of the available bDMARDs in this setting, the choice of the second bDMARD is made on an individual basis and influenced by several reasons, including the cause of discontinuation of the first TNFi, previous drugs, concomitant therapy and comorbidities.

In case of non-response to an original biological, switching to its biosimilar should not be done.

The existence of limited data regarding switching from a non-TNFi agent to another bDMARD (TNFi or another), does not allow for a specific recommendation.

**RECOMMENDATION 9**

In case of sustained remission, tapering bDMARD can be considered, especially in patients with concomitant csDMARDs treatment. No specific recommendations about tapering regimens can be made at the moment.

Since 2011, several studies have demonstrated that bDMARDs can be tapered or even stopped without causing flares in a considerable percentage of patients\textsuperscript{137-143}. In established RA, the available data suggest that many patients flare upon withdrawal of a TNFi, while those who tapered bDMARD more frequently maintain low disease activity and present less radiographic progression\textsuperscript{142,144,146}. In the PRESERVE trial, patients assigned to receive etanercept (25 mg/wk) continued to have low disease activity in the double-blind period whereas those who received placebo (maintenance of csDMARDs) had a mean disease activity in the moderate range. The groups given etanercept (50mg/wk or 25mg/wk) kept similar patterns of response, and maintained a better efficacy than the group given placebo\textsuperscript{145}. Similar findings were obtained in other studies\textsuperscript{144,146}.

Contradictory results were observed in early arthritis. In the PRIZE trial, after attainment of sustained remission in early RA, dose reduction of etanercept, but not the withdrawal of the biologic, was accompanied by maintenance of response, with 63.5 % of patients remaining in remission (DAS28<2.6 at week 76 and 91 visits)\textsuperscript{143} while in the open label extensions of OPTIMA\textsuperscript{147} and HIT HARD\textsuperscript{138} studies, patients who withdrew the biologic agentbDMARD plus methotrexate, maintained good clinical\textsuperscript{138,147}, radiographic\textsuperscript{138,142} and functional response\textsuperscript{147}.

Even though most studies on dose reduction or withdrawal have been performed with TNFi, data on other bDMARDs (abatacept and tocilizumab) are emerging with similar overall results. However, the percentage of patients in remission at the end of the withdrawal studies has been small, ranging from 9 to 44\%\textsuperscript{68,104,146,151}. Only one observational cohort study\textsuperscript{152} evaluated dose reduction of tocilizumab, yielding at the end of the 24-week study, 55% of patients in low disease activity.

In early arthritis, more profound and persistent response increases the likelihood of maintenance of a good outcome after withdrawal of a bDMARD, maintaining therapy with csDMARDs\textsuperscript{153}.

Gradual bDMARD dose reduction may be a better strategy than abrupt discontinuation\textsuperscript{143,146,154}. In case of relapse, reintroduction of the bDMARD appears to allow the return to a favorable outcome\textsuperscript{68,133,155,156}. Importantly, before bDMARDs tapering, glucocorticoids should be withdrawn\textsuperscript{2}.

**RECOMMENDATION 10**

bDMARD should be avoided in pregnant and breastfeeding women.

If pregnancy occurs, it is advisable to stop bDMARD.

In some cases, based on shared decision between patient and physicians (rheumatologist and obstetrician), TNFi therapy can be considered in early stages of pregnancy.

There is no indication to stop bDMARD in males who wish to become parents.

Based on animal and human tests, the US Food and Drug Administration (FDA) established pregnancy risk categories of drugs\textsuperscript{157}. TNFi are considered category B. Tocilizumab, rituximab and abatacept are considered category C\textsuperscript{157,158}. The majority of evidence comes from observational studies. Randomized clinical trials are difficult to implement in this field due to ethical aspects. The use of all these drugs in pregnancy is contraindicated by the manufacturer and contraception is indicated in women receiving them.

TNFi agents are neither teratogenic in animals nor mutagenic in pre-clinical tests\textsuperscript{158}. Results from several observational studies over the last years, mainly in women with inflammatory bowel disease (IBD) but also in inflammatory rheumatic diseases (IRD), showed that TNFi exposure before or during pregnancy was not associated with increased risk of miscarriage or congenital malformations\textsuperscript{159-168}.

Nevertheless, it is advisable to stop TNFi when
pregnancy is confirmed; its continuation can be considered in patients with active disease. The benefits of TNFi in controlling disease and achieving remission seem at current knowledge to outweigh the theoretical risk of fetus exposition to the drug. The decision should be shared between patient and physicians (rheumatologist and obstetrician), balancing risks and benefits.

Difference in placental transfer related to molecule structure, half-life and monotherapy indication should be considered regarding the different TNFi drugs. Infliximab and adalimumab, are both IgG1 antibodies, being transported across placenta (minimal during first trimester and increasing during the remaining pregnancy). Etanercept, a dimeric fusion protein linked to IgG1Fc portion, has very low trans-placental passage. Certolizumab pegol, a PEGylated, humanized antigen-binding fragment of an anti-TNF antibody is not actively transported across placenta; however the Fab fragment can cross placenta in very low levels. Based on these data, certolizumab pegol can be maintained until the end of the second trimester, if necessary, while other TNFi should be stopped until the end of the first trimester. More data regarding golimumab is required to state any recommendation.

The administration of TNFi should be avoided in the third pregnancy trimester, but more studies are needed to evaluate the effects of using biologics throughout pregnancy.

Data for other bDMARDs (golimumab, rituximab, abatacept and tocilizumab) are scarce. It is advisable to stop the drug before conception, respecting the wash-out period before drug discontinuation and pregnancy, which will vary according the drug.

Data regarding male exposure to TNFi at conception is limited. Small observational studies did not show any negative impact regarding live births or congenital abnormalities. Based on these data, bDMARDs should be avoided during lactation due limited or absent data regarding its safety.

**GENERAL SAFETY CONSIDERATIONS**

**bDMARD THERAPY ARE CONTRA INDICATED IN THE FOLLOWING SITUATIONS:**

1) Active infection (including opportunistic infection, active tuberculosis, HIV, HCV and HBV infections)

2) Malignancy:
   - Current or recent history of cancer (≤5 years), except basal and squamous cell skin cancer after complete excision
   - No recommendations are possible at this moment regarding pre-malignant conditions
   - In some cases, Rituximab can be considered (see recommendation 7). The use of other non-anti-TNF agents can be considered in individual cases based on benefit/risk assessment

3) Concurrent administration of live vaccines
4) Heart Failure (NYHA Class III or IV), in case of anti-TNF treatment
5) Demyelinating disease, except rituximab that can be used in some situations

**TUBERCULOSIS SCREENING BEFORE INTRODUCTION OF BIOLOGICAL THERAPIES**

Evaluation for latent and active tuberculosis should be performed in all patients with joint inflammatory diseases before starting bDMARDs in accordance with the recommendations developed by SPR and the Portuguese Society of Pneumology.

**CRITERIA FOR TEMPORARY SUSPENSION/POSTPONEMENT OF INTRODUCTION OF BIOLOGICAL THERAPIES**

This issue is detailed in the practical guide for prescribing biological therapies published by SPR.

**CONCLUSION**

bDMARDs reflects an advance in the approach of RA patients. Its use plays an important role in RA treatment, leading to better outcomes. These updated recommendations reflect the new evidence on efficacy and safety published since 2011.

The use of bDMARDs should be monitored regularly, regarding clinical efficacy and safety. Remission or at least low disease activity should be the treatment target. Precautions related to adverse events and contra-indications should be considered when these drugs are used.

New drugs are being developed [Janus kinase (JAK) inhibitors, IL-6 antagonists, and others], thus these recommendations should be updated when new evidence become available.

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