

Strategies for the withdrawal of classic and biological DMARD in clinically inactive patients with juvenile idiopathic arthritis

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Dear Editor,

The disease-modifying anti-rheumatic drugs (DMARDs) significantly altered the natural course of Juvenile Idiopathic Arthritis (JIA), allowing a state of clinical inactivity in most patients. When remission is reached, many clinicians attempt to withdraw these drugs¹. However, there are no guidelines for this purpose.

The rationale of our study was to describe how Portuguese rheumatologists and pediatricians manage patients with JIA in clinical inactive disease (CID). To this end, we developed an anonymous survey with 30 questions inquiring the importance of some factors when considering the withdrawal of DMARDs. This survey was sent to all the 35 clinicians enrolled in the Portuguese group of pediatric rheumatology.

CID was defined according to the classification of Wallace *et al.*²: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy; no active uveitis; normal erythrocyte sedimentation rate or C-reactive protein; and a physician's global assessment of disease activity rated at the best score, and morning stiffness less than 15 minutes.

Due to a very different presentation and evolution from other JIA subtypes, systemic JIA was excluded, which also allowed to compare with other studies.

Twenty-three complete responses were obtained, 14 from rheumatologists and 9 from pediatricians exercising pediatric rheumatology, with a mean clinical experience of 14.1 (± 8.7) years.

Similar to other studies³, the factors with the greatest impact on the decision to withdraw cDMARDs were the duration of CID, the therapy-induced toxicity, the presence of erosive disease and joint damage, the subtype of JIA, the time to reach inactive disease, and the

low adherence to therapy. These factors were classified as "very important" by more than 50% of the clinicians. The same factors, except for low adherence, had the greatest impact when considering the withdrawal of bDMARDs (Figure 1A). We hypothesize that low adherence has less influence on the withdrawal decision of bDMARDs, since their supply is controlled by the hospital-pharmacy and so adherence will be greater.

The subtype of JIA was reported to influence the decision to withdraw cDMARDs and bDMARDs by 95.2% and 87.5% of the clinicians, respectively. In fact, withdrawal was more likely in patients with persistent oligoarticular JIA, followed by extended oligoarticular, enthesitis-related arthritis, rheumatoid factor (RF) negative polyarticular, psoriatic arthritis, and less likely in RF positive polyarticular JIA. Regarding the therapy used, 76.2% considered that the type of cDMARD influences the suspension decision, with sulfasalazine being more susceptible to be discontinued than methotrexate. Only 6.2% answered that the type of bDMARD used would influence their decision.

Most participants reported that they usually begin the drug withdrawal only after 12 months of sustained remission, by progressively tapering the dose of the cDMARD or spacing bDMARD doses (Figure 1B). This difference on the withdrawal strategy may be explained by the lack of formulations with different doses of bDMARDs in contrast with cDMARDs. Moreover, Portuguese clinicians appear to have a more conservative strategy in comparison to other studies, where physicians only waited 6 to 12 months after CID³. However, according to Klotsche *J et al.*, remission for more than 12 months before drug withdrawal seems to be associated with a lower rate of disease relapse⁴.

Also, participants reported that the decision to suspend the DMARD was based on imaging methods, preferably ultrasound, and in patient-reported outcomes (Figure 1C).

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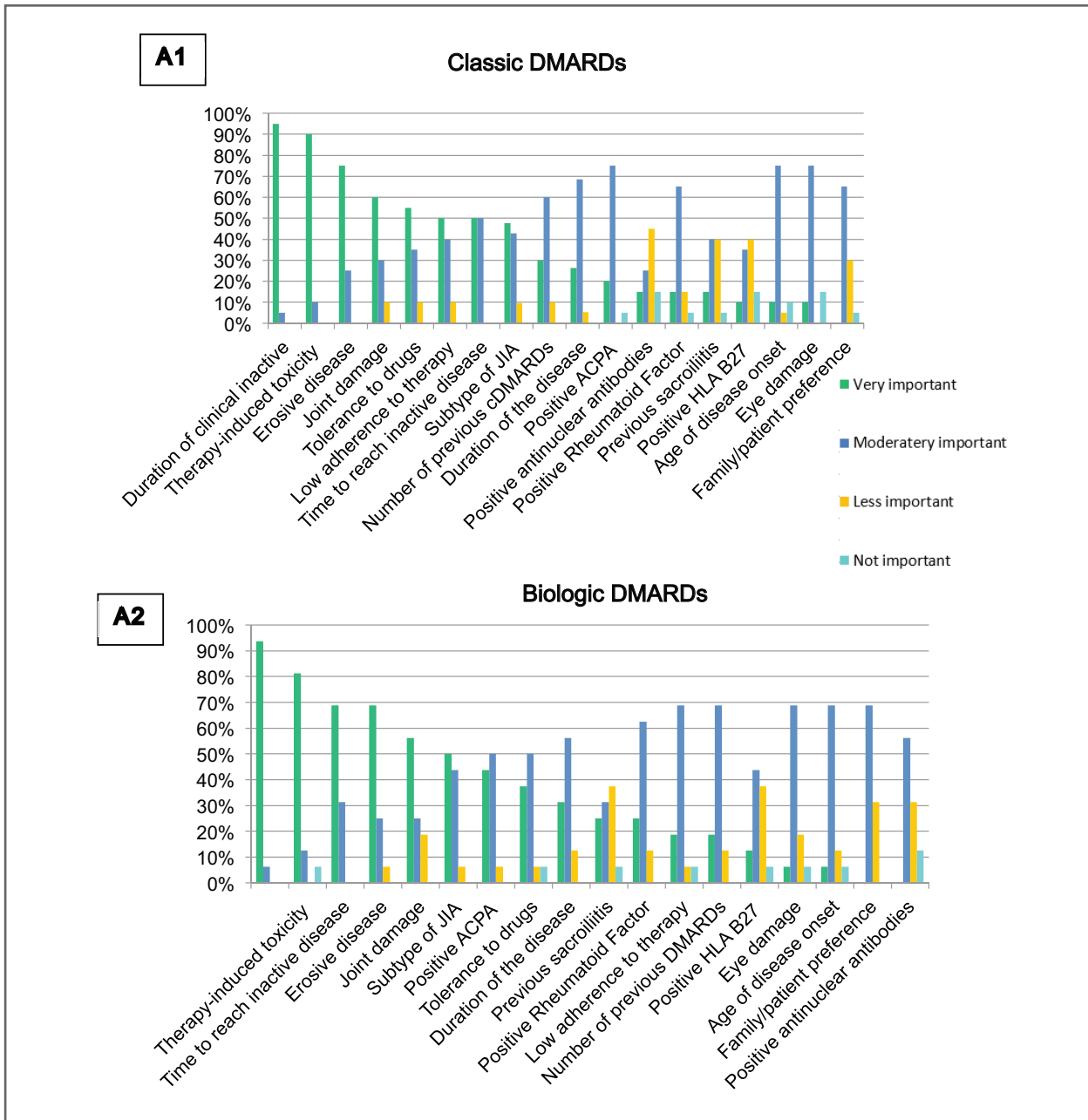


FIGURE 1. A: Factors with the greatest impact on the decision to suspend classic (A1) and biological (A2) DMARDs. B: Ways to suspend DMARDs. C: Ancillary tests that influenced decision-making to withdraw DMARDs: imaging (C1), patient-reported outcome (C2). ACPA: Anti-citrullinated peptide antibody; CHAQ: Child Health Assessment Questionnaire; DMARDs: disease-modifying anti-rheumatic drugs; PGA: Parent/Patient Global Assessment

For patients on combination therapy, bDMARDs are reported to be the first to be withdrawn by 73.3% of the participants, while in other studies, the majority prefer to discontinue methotrexate first³.

It has been speculated that high serum levels of the S100A8/A9 (calprotectin or MRP8/14), S100A12 and

DEK autoantibody may indicate subclinical inflammation and predict the risk of flare after DMARDs suspension. However, studies showed controversial results so it cannot yet be used in clinical practice⁵⁻⁷.

Literature is scarce on this matter and there are no well-defined guidelines on how to withdraw cDMARDs

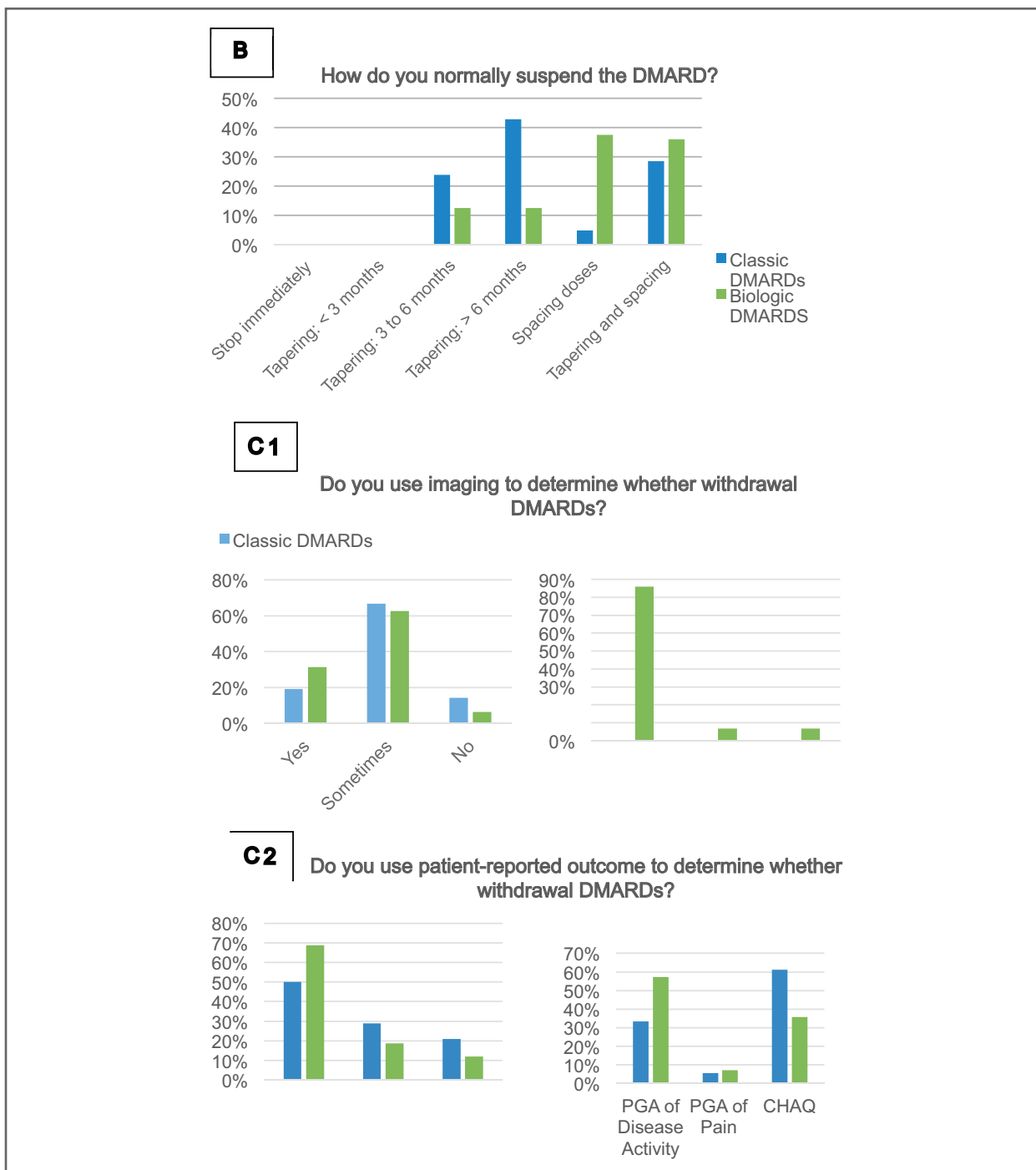


FIGURE 1. continuation

or bDMARDs in JIA. Notwithstanding, most Portuguese physicians were in agreement on the factors that need to be considered with respect to this decision. Moreover, this finding follows the same line of

thought reported in similar studies carried out in foreign countries. Our study portrays Portuguese reality and may help to develop withdrawal strategies in the future.

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