Ultrasound assessment as predictor of disease relapse in children and adults with arthritis in clinical stable remission: new findings but still unmet needs

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Several lines of evidence suggest that imaging plays an important role in the diagnosis and monitoring of patients with juvenile idiopathic arthritis (JIA) leading the European League against Rheumatism (EULAR)–Paediatric Rheumatology European Society (PReS) to develop as point to consider the use of imaging within the JIA assessment in clinical practice.[1] The use of ultrasound (US) may increase the sensitivity of clinical examination through its ability to detect joint inflammation (in terms of synovial hypertrophy, joint effusion and power Doppler (PDUS) activity) in case of clinically inactive disease.[2–4] In particular, it has been shown that the majority of patients with JIA in clinical remission may exhibit greyscale (GSUS) abnormalities and in half of them the presence of PDUS signal can be found,[4] without any significant difference on the basis of the pharmacological treatment scheme through which the remission was achieved[2–4] and even in case of drug-free remission (DFR).

In *ARD*, De Lucia *et al* analysed the predictive power of US assessment to foresee disease flare in patients with JIA in clinical remission.[5] The authors included 88 consecutive patients with JIA, stratified based on the joint involvement, undergoing US assessment (including GSUS and PDUS) of 44 joints, finding that nearly one-fourth of them showed US abnormal findings despite clinically inactive disease, mainly in patients with extended joint involvement and with shorter period of time from remission achievement (less than 6 months). Interestingly, during the 4 years of follow-up, almost half of patients with JIA experienced a disease flare with the higher rate of relapse in patients with JIA with residual PDUS synovitis at the time of remission achievement. These can be considered relevant findings since previous studies failed to confirm the predictive value of US assessment in foreseeing the chance of disease flare in JIA.[6 7] In particular, Magni-Manzoni *et al* evaluated 39 patients with JIA showing that US-detected synovitis is a common finding in children in clinical remission and its presence does not predict an early flare in the affected joints.[6] Similarly, Zhao *et al* recently confirmed in a comparable study cohort of children with JIA that nearly half of them have abnormal US findings whose presence is not associated with subsequent clinical flare in up to 2 years of follow-up.[7] Moreover, the EULAR/PreS points to consider do not include a proposal list of the joints sites eligible for US assessment to increase the ability to detect subclinical ongoing inflammation despite clinical sustained remission in children. In particular, Breton *et al*[8] assessed the II–V metacarpophalangeal and I–V metatarsophalangeal (MTP) joints in children with JIA and in healthy controls detecting features of synovitis (defined as synovial thickening with or without effusion and hypervascularity) mainly in MTP joints of children with JIA without any clinical sign of inflammation. The study by De Lucia *et al*[5] provides additional information having performed a more extensive US assessment, including 44 joints, which may significantly increase the accuracy of disease activity determination in children in whom subjective symptoms may be underestimated compared with adult patients. In adults with rheumatoid arthritis (RA), the EULAR/Outcome Measures in Rheumatology (OMERACT) group have developed a standardised combined scoring system, including both GSUS–PDUS components, in the evaluation of synovitis in multiple joints with high reliability when applied in scanning patients but still lacking a defined optimal reduced joint set to be evaluated in clinical practice as well as in clinical trials.[9 10] The manuscript by De Lucia *et al*[5] therefore differentiates itself from the previous ones in being much more stringent in its methodology and it raises the need to use GSUS and PDUS parameters in a complementary manner to detect more precisely the entity of residual inflammation of the target tissue in children with inactive disease, strongly supporting its use as a useful tool in clinical practice.

USE OF ULTRASONOGRAPHIC AND STRICT CLINIMETRIC COMBINED CRITERIA FOR THE IDENTIFICATION OF RESIDUAL SYNOVITIS IN ADULT PATIENTS WITH RA IN STABLE CLINICAL REMISSION

Stable clinical remission is the most important goal in children with arthritis as well as in adults with RA,[11] but despite apparent clinical remission, defined with composite indices such as DAS (Disease Activity Score),[12] joint damage progression can occur.[13] This issue is tightly related to the current lack of uniform definition of sustained remission in adults with RA.[14] The ACR/EULAR definition certainly has improved our confidence in defining a patient in remission in clinical trials, yet some issues still need to be defined in clinical practice.[14 15]

It is known that US assessment, through GSUS and PDUS evaluation, is able to identify residual synovitis in more than 50% of adult patients with RA in clinical remission on the basis of their DAS value.[13] When comparing the PDUS-negative and PDUS-positive patients with RA in DAS remission, in a real-world setting, significantly fewer PDUS-negative patients with RA in clinical remission experienced a flare during 12 months of follow-up, compared with patients with RA with PDUS positivity at the time of remission achievement.[16 17] Recently, Zufferey *et al*,[18] in a multicentre cohort study including adult patients with RA in DAS28-selected clinical remission, confirmed an incidence of US-detected residual synovitis in more than half of enrolled RA confirming the use of US, yet the assessment of US positivity yielded a moderate predictive power for loss of remission in a real-life setting. A longitudinal study evaluating the combined use of serial US assessment in long-standing adult patients with RA in clinical remission showed an increase

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in the success rate of maintaining disease control after anti-tumour necrosis factor tapering and discontinuation compared with only DAS-based selection.[19]

The histological characteristics of synovial tissue residual inflammation have been described in patients with RA in sustained DAS-defined and US-defined remission.[20] Moreover, the use of a stricter selection criterion as the Simplified Disease Activity Index (SDAI) enables a more precise identification of patients with RA in sustained disease control with histopathologically minimal synovitis and significantly lower chance of disease relapse after treatment de-escalation. These findings support the concept that the fulfilment of the SDAI-based remission status, combined or not with US remission criterion, reduces the relapse rate after treatment modifications in adults with RA. This should be demonstrated also in JIA at the same extent.

USE OF COMBINED SEROLOGICAL AND IMAGING BIOMARKERS FOR THE IDENTIFICATION OF PATIENTS WITH ARTHRITIS IN STABLE CLINICAL REMISSION WITH HIGH RISK OF DISEASE RELAPSE AFTER TREATMENT TAPERING/DISCONTINUATION

In addition to the use of US assessment for the identification of patients with RA eligible to treatment tapering and discontinuation, once stable clinical remission is achieved, serological biomarkers such as anticitrullinated peptide antibody (ACPA) positivity independently associated with disease flare after treatment discontinuation[21] and with lower chance of achieving (persistent) DFR.[22 23] To date, limited information are available on predictive biomarkers of disease relapse in ACPA/rheumatoid factor (RF)-negative patients with RA. An abnormal Multi-Biomarker Disease Activity panel arose to identify patients with RA in clinical remission, despite their serological status, with higher risk of disease relapse because of residual synovitis.[24] To date, no comparable studies have been conducted in patients with JIA in sustained remission; therefore, the results obtained by De Lucia *et al*,[5] showing a strong predictive value of US assessment, suggest its possible inclusion as instrumental criterion for remission definition in patients with JIA, which could increase the success rate of treatment de-escalation. However, it should be taken into account also that US is not able to predict disease flares in all patients, needing certainly further standardisation and mostly biomarkers capable of defining a deeper remission.

UNMET NEEDS FOR THE GLOBAL DEFINITION OF CLINICAL REMISSION AND FOR A WISER STRATEGY FOR MEDICATION TAPERING AND DISCONTINUATION IN JIA

More complicated is the issue about the definition of clinical remission in JIA since it consists of a heterogeneous group of conditions involving synovial tissue and even extra-articular domains. Moreover, the clinical course of JIA is unpredictable, with periods of low disease activity followed by recurrence of signs and symptoms on or off medications.[25] The probability of achieving inactive disease and/or clinical remission in JIA seems to be tightly related to the clinical subtype.[26] Children with RF-positive polyarthritis showed a lower overall remission rate after treatment compared with children with oligoarticular-persistent JIA.[27] These data are supported by the US findings, provided by De Lucia *et al*, showing a lower likelihood of US-detected residual synovitis in the latter group.[5] In fact, in the study by De Lucia *et al*,[5] US-detected residual synovitis was more significant in patients with JIA with more extended joint involvement despite no information provided on its incidence in relation to the presence of extra-articular manifestations. This is indeed a question that this study raises, suggesting the need to include multiple domain evaluation within the global assessment of children with JIA in remission. However, once disease remission is achieved in children, limited evidences are available about the predictors of disease flare. Among them, RF positivity was found to be an independent parameter associated with disease flare after attaining inactive disease together with a severe disease course (defined as an active joint count >4, use of biologics and patient global assessment >30 mm),[28] and abnormal C reactive protein.[29] Conversely, contradictory data are available on the predictive role of antinuclear antibody (ANA) positivity whose presence was associated with a higher risk of flare by Guzman *et al*,[28] whereas in a previous prospective study conducted by Miotto e Silva *et al*, patients with JIA who flared during the follow-up were not different in terms of ANA positivity compared with subjects who maintained disease control during the follow-up.[30] Limited data are available about the best strategy to taper or discontinue pharmacological treatment in children with JIA once clinical remission is achieved and stably maintained. Systematic literature analysis including published studies carried out on adults with RA showed that biological disease modifying anti rheumatic drugs (bDMARDs) discontinuation leads to an increased risk of losing remission or Low Disease Activity status and an increased risk of radiographic damage progression compared with treatment continuation.[31] The best modality of treatment tapering in adults with RA is still a matter of debate since both the reduction of drug dose and the increase of application interval (spacing) are suggested in adult patients with RA in persistent remission.[11] More exhaustive information will be provided by the analysis of currently ongoing trials, comparing different modalities of treatment reduction (early vs late reduction, respectively) in adults with RA in stringent clinical remission (Clinical Disease Activity Index ≤2.8),[32] despite no systematic data on this issue available so far for children with JIA.

In conclusion, the research agenda should aim to a more comprehensive definition of disease remission for children with arthritis. This goal could be reached through multiple comparison studies aiming at defining the global profile of 'the patient' with arthritis in remission and then eligible to treatment tapering or discontinuation reducing at minimum the risk of disease flare. Therefore, US assessment, which has been shown to be a useful tool to determine subclinical activity in patients in sustained clinical remission, should be included along with other possible biomarkers—in studies aiming at the definition of the best matrix able to identify the long-term drug-free remission prognosticators regardless of the patient's age.

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REFERENCES

1 Colebatch-Bourn AN, Edwards CJ, Collado P, *et al*. EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. *Ann Rheum Dis* 2015;74:1946–57.
2 Nielsen HE, Strandberg C, Andersen S, *et al*. Ultrasonographic examination in juvenile idiopathic arthritis is better than clinical examination for identification of intraarticular disease. *Dan Med J* 2013;60:A4669.
3 Rebollo-Polo M, Koujok K, Weisser C, *et al*. Ultrasound findings on patients with juvenile idiopathic arthritis in clinical remission. *Arthritis Care Res* 2011;63:1013–9.
4 Bugni Miotto e Silva V, de Freitas Tavares da Silva C, de Aguiar Vilela Mitraud S, *et al*. Do patients with juvenile idiopathic arthritis in remission exhibit active synovitis on joint ultrasound? *Rheumatol Int* 2014;34:937–45.
5 De Lucia O, Ravagnani V, Pregnolato F, *et al*. Baseline ultrasound examination as possible predictor of relapse in patients affected by juvenile idiopathic arthritis (JIA). *Ann Rheum Dis* 2018:annrheumdis-2017-211696.
6 Magni-Manzoni S, Scirè CA, Ravelli A, *et al*. Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. *Ann Rheum Dis* 2013;72:223–8.
7 Zhao Y, Rascoff NE, Iyer RS, *et al*. Flares of disease in children with clinically inactive juvenile idiopathic arthritis were not correlated with ultrasound findings. *J. Rheumatol* 2018;45:6.
8 Breton S, Jousse-Joulin S, Cangemi C, *et al*. Comparison of clinical and ultrasonographic evaluations for peripheral synovitis in juvenile idiopathic arthritis. *Semin Arthritis Rheum* 2011;41:272–8.
9 Terslev L, Naredo E, Aegerter P, *et al*. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce—Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open* 2017;3:e000427.
10 D'Agostino MA, Terslev L, Aegerter P, *et al*. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce—Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017;3:e000428.
11 Smolen JS, Landewé R, Bijlsma J, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.
12 Mierau M, Schoels M, Gonda G, *et al*. Assessing remission in clinical practice. *Rheumatology* 2007;46:975–9.
13 Yoshimi R, Hama M, Takase K, *et al*. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. *Mod Rheumatol* 2013;23:456–65.
14 Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
15 Baker KF, Pratt AG, Thompson B, *et al*. Let's not fool ourselves. In RA, the ACR/EULAR remission criteria are not perfect!. *Ann Rheum Dis* 2017;76:e12.
16 Peluso G, Michelutti A, Bosello S, *et al*. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis* 2011;7:172–5.
17 Naredo E, Valor L, De la Torre I, *et al*. Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. *Rheumatology* 2015;54:1408–14.
18 Zufferey P, Scherer A, Nissen MJ, *et al*. Can ultrasound be used to predict loss of remission in patients with RA in a real-life setting? A multicenter cohort study. *J Rheumatol* 2018;15.
19 Alivernini S, Peluso G, Fedele AL, *et al*. Tapering and discontinuation of TNF-α blockers without disease relapse using ultrasonography as a tool to identify patients with rheumatoid arthritis in clinical and histological remission. *Arthritis Res Ther* 2016;18:39.
20 Alivernini S, Tolusso B, Petricca L, *et al*. Synovial features of patients with rheumatoid arthritis and psoriatic arthritis in clinical and ultrasound remission differ under anti-TNF therapy: a clue to interpret different chances of relapse after clinical remission? *Ann Rheum Dis* 2017;76:1228–36.
21 Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:S100–8.
22 Haschka J, Englbrecht M, Hueber AJ, *et al*. Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis* 2016;75:45–51.
23 van den Broek M, Dirven L, Klarenbeek NB, *et al*. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. *Ann Rheum Dis* 2012;71:245–8.
24 Rech J, Hueber AJ, Finzel S, *et al*. Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment. *Ann Rheum Dis* 2016;75:1637–44.
25 Glerup M, Herlin T, Twilt M, *et al*. Clinical outcome and long-term remission in JIA. *Curr Rheumatol Rep* 2017;19:75.
26 Selvaag AM, Aulie HA, Lilleby V, *et al*. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. *Ann Rheum Dis* 2016;75:190–5.
27 Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290–4.
28 Guzman J, Oen K, Huber AM, *et al*. The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort. *Ann Rheum Dis* 2016;75:1092–8.
29 Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, *et al*. Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. *Arthritis Care Res* 2013;65:1112–20.
30 Miotto e Silva VB, Mitraud SAV, Furtado RNV, *et al*. Patients with juvenile idiopathic arthritis in clinical remission with positive power Doppler signal in joint ultrasonography have an increased rate of clinical flare: a prospective study. *Pediatr Rheumatol Online J* 2017;15:80.
31 Henaux S, Ruyssen-Witrand A, Cantagrel A, *et al*. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. *Ann Rheum Dis* 2018;77.
32 Glinatsi D, Heiberg MS, Rudin A, *et al*. Head-to-head comparison of aggressive conventional therapy and three biological treatments and comparison of two de-escalation strategies in patients who respond to treatment: study protocol for a multicenter, randomized, open-label, blinded-assessor, phase 4 study. *Trials* 2017;18:161.