CONSIDERATIONS ABOUT BIOLOGIC TREATMENT WITHDRAWAL IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS AFTER DISEASE REMISSION

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Abstract

The aim of this paper is to discuss the reasons and opportunities for tapering and discontinuing treatment with biological agents when the clinical remission of juvenile idiopathic arthritis (JIA) is achieved. Unfortunately, the few studies published recently on JIA focused almost exclusively on etanercept and had conflicting results. It appears that the relapse rates after termination of these medications is substantial. No predictors of the risk of flare were identified. Currently, the role of Doppler ultrasound in the assessment of the status of JIA (activity/remission) has not been fully established. The optimal timeline for withdrawal after documentation of remission, as much as the modality of discontinuation, also remain to be established. The lack of evidence-based data from randomized controlled clinical trials imposes a pressing need to create guidelines for treatment discontinuation.

Keywords: JIA, biological treatment, withdrawal

"There is a reason behind everything."
(Aristotle)

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA), like others rheumatic diseasesresulting from deregulation of normal body constituents with unknown etiology, is still considered "incurable" (1).The joint damage results from continuous inflammation over extended periods of time. So, patients need long intervals (sometimes life-long) of treatment with multiple medications, such asconventional disease modifying anti-rheumatic drugs (DMARDs) or highly effective biological agents (in the last two decades) in order to target and to maintain a state of "low disease activity" or "remission", terms well defined (2-4). Biologic agents have indeed revolutionized the treatment and outcomes of patients with JIA. Achieving inactive disease has become increasingly more common in pediatric rheumatology practice. This success, combined with the potential side effects and high drug-costs of continued biologic treatment, lead to consideration of drug discontinuation in some patients (5). This is why the pressure on the pediatric rheumatologists for a possible discontinuation of therapies has such great importance. "Once complete disease quiescence has been achieved, it would be desirable to discontinue ongoing treatment to avoid prolonged exposure of the child to the potential of adverse effects. This goal should be balanced with the risk of disease flare after withdrawal of therapy" (6). Unfortunately, no evidence-based data, guidelines or expert recommendations are available for the safe discontinuation of medications after achievement of inactive disease status.

BIOLOGIC TREATMENT WITHDRAWAL: REALITIES AND PERSPECTIVES

Most of the studies have focused on tumor necrosis factor α (TNF-α) inhibitors such as etanercept, which are currently the anti-rheumatic medication

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most frequently used in children with chronic arthritis and in several countries the only one available. Rates of inactive disease after biological treatment, based on data from National Registries or from a single-center series, were similar for many of these agents. For etanerceptit was reported as 37-49% (7), 47.6% (8), 50.3% (9) and 50% (10). Clinical remission rates in my hospital were 46%, with 18 of 39 patients treated with etanercept achieving more than ACR70 (unpublished data). There is a limited number of retrospective publications studying the effects of discontinuing treatment in children with JIA attaining a state of clinical remission. Many of these studies have in common clinical remission on treatment lasting more than 12 months, most of them comparing the abruptly versus gradual discontinuation and their effect on the rate of flare phenomena. The children in whom etanercept was discontinued with no or a too short period of inactive disease experienced more frequentlya disease flare. "The patients should meet criteria for clinical remission on medication for at least 1.5 years before the discontinuation of etanercept and it should be withdrawn gradually" (11). Conversely, no association was observed between the duration of inactive disease prior to discontinuation of etanercept and the method of treatment discontinuation and the time to disease relapse (12). The same findings were reported by others authors (13,14). After cessation of etanercept administration, 69% of patients relapsed after a mean 5.8 months (12), and similarly, in another study only 30.8% of patients did not develop disease exacerbation until the end of follow-up at a mean of 25.4±12 months (range 16-60) (14). The same authors proposed that low doses of etanercept might be sufficient to maintain remission (12). The subset of patients at high risk for disease relapse might need a longer etanercept administration to maintain remission (14). In contrast, the results of a large retrospective study with 171 patients suggest that prolonged treatment with TNF-α antagonists does not increase the *likelihood* of sustained remission after withdrawal of therapy (15). Cai et al. also used the step-down method for etanercept tapering. During the first year of the study the dose of etanercept was kept at 0.4 mg/kg/week, which is half the dose of what those patients received previosly. During the second year the dose of etanercept was further lowered to 0.4 mg/kg/month.The cumulative flare rate was 12.9% at 12 months and then unchanged in the second year (16).

Currently there is no data regarding the discontinuation of other biologic agents used in children with JIA such as adalimumab, abatacept, tocilizumab, anakinra, orcanakinumab. In a personal unpublished case of systemic JIA, the first attempt to gradual discontinuation increasing the interval between administration of anakinra after one year of clinical remission, the disease relapsed and continuous treatment had to be restarted. A new attempt after two years succeeded using the same method of withdrawal. It is not yet established if it is better to stop treatment abruptly or to taper it gradually, either by reducing the dosage progressively or by increasing the interval between doses. Although there are no significant differences between the two methods, some experts suggest a gradual strategy for biologic agents. However, on the basis of immunogenicity associated with gradual withdrawal, it seems to be rationale to proceed to relatively abrupt discontinuation of biological agents (1). Nevertheless, pediatric rheumatologists remain cautious about the discontinuation of treatment. Southwood et al discontinued etanercept treatment only in 100 (20,7%) of 483 patients with JIA, most of them (88) because of treatment failure and only 9 after disease control.

The same problems have been debated for rheumatoid arthritis (RA), this type of approach resembling to treatment paradigms used in other disciplines, such as the "induction-consolidation" treatment approach used for certain malignancies (1). The experience of adult rheumatologists in this areais definitely more extensive than that of pediatricians. Because the evidence-based data and expert recommendations to guide medication discontinuation in JIA are not yet available it is advisable, at least for some cases and situations, to extrapolate the reasonable principles used for RA and resumed in the next paragraphs. Most patients currently treated for inflammatory rheumatic diseases receive a combination of at least two medications: a synthetic remissive and a biologic agent. In general, a discontinuation program must be gradual with a plan for all medications, but it should not involve all medications at one time. This approach provides evidence to the physician and the patient that the ultimate goal of total withdrawal of medication might be possible (1). A long-term program of medication withdrawal is desirable, often with a comprehensive plan for all medications, one or two agents might be retained indefinitely (e.g., weeklyanti-inflammatory low-dose methotrexate, one of the safest medications). Usually,

based on costs, and also to minimize risk of potential adverse events, the biological agent should be the first to be discontinued (idem). Quantitative assessment response to therapy, and discontinuation of therapy, according to quantitative indices rather than narrative descriptions, is mandatory.

Another important aspect is that of the difficulty identifying the optimal individual treatment and predicting outcomes for each patient, the rates of "successful" discontinuation pertaining to groups of patients. Many patients represent exceptions from trends identified in groups (1). The first principle of "treat-to-target" paradigm in RA is that the treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist (5). Extrapolating to JIA, the decision for discontinuation has to be shared between the patient's family or patient and the pediatric rheumatologist, explaining criteria for initiating discontinuation, benefit and risk, criteria for successful discontinuation etc. (1).

A rational approach to treatment discontinuation once inactive disease status has been achieved would require the capacity to predict which subset of patients will successfully attain sustained clinical remission and which subset will experience disease flares (6). Unfortunately, except for the levels of myeloid-related proteins 8 and 14 (MRP8/14), a biomarker associated with a low risk of flares after treatment discontinuation of methotrexate when its levels were low, and reversely, higher concentrations with imminent risk of relapse (18,19), no predictor of disease course after treatment discontinuation was identified (14-16).

The synovit is detected by imaging in adults with RA in clinical remission and vascularization detected by Doppler ultrasound considered to predict short-term disease flare after clinical remission (20-23), was also observed in a sizable proportion of JIA patients classified as having inactive disease by clinical criteria. While in RA these findings may be included in future remission criteria, in JIA the clinical significance and prognostic value of these abnormalities did not predict subsequent synovitis flare (24-26). The current explanation for this distinction is the difficulty to establish whether the presence of juxta-articular flow at power Doppler examination in the growing child represents normal flow to the well-vascularized cartilage of the epiphysis or synovial hyperemia indicating inflammation. This finding suggests that residual synovitis on imaging should not lead to treatment in the absence of clinical indications. Brown et al. used 3 TMRI with contrast enhancement to compare two small cohorts of patients with JIA and RA in clinical remission. They found that 63% of the JIA and 70% of the RA had subclinical disease (synovitis, bone marrow lesions, and/or tenosynovitis) despite clinical remission (27). However, more information from healthy children is needed to enable differentiation of the bone and cartilage abnormalities that reflect damage from those that are part of normal development using MRI or ultrasonography (28). While outcomes are improved with newer agents, there is no evidence that the autoimmune process or inducing immunologic tolerance are fundamentally altered and therefore the disease may continue as a smoldering disease. "The long-term implications of this disease activity remain unknown at present, but it is possible that smoldering subclinical RA may have an impact on functional status over the years" (29). But, if we accept the persistence of subclinical disease in those patients that fulfill criteria for clinical remission, the new paradigm of biological treatment discontinuation itself seems to be unreasonable.

CONCLUSIONS

Achieving inactive disease has become increasingly more common in pediatric rheumatology practice, mainly in JIA. This success and the potential side effects and high drug costs of continued biologic treatment has imposed the need for drug discontinuation in such cases. Moreover, this may promote better compliance to treatment. If the benefits can be achieved with shorter treatment courses, access to the biological agents may be optimized (29). For socio-economic reasons, if the withdrawal will not be possible in the future, the only acceptable alternative to reduce the costs will be the development and approval of biosimilars.

The rare studies published recently on JIA had conflicting results, so definitive conclusions or recommendations are not yet available. Unfortunately, guidelines exist only for the initiation of biological drugs, but not for their discontinuation. Therefore, the decision is left up to practitioners in order to decide whether it is more advantageous to stop treatment abruptly or gradually by reducing the dosage progressively or by increasing the interval between doses. Family/patient choice is another critical component of treatment paradigms (29). Once biologic agents are discontinued, the monitoring of disease activity, functional ability and radiological damage

progression is mandatory. The restart of treatment as soon as disease is relapsing is also mandatory (30, 31). The need for randomized controlled trials, analyses of clinical databases, and expert recommendations to guide discontinuation of therapy is critical in this setting.

REFERENCES

1. **T. Pincus, J. Braun, A. Kavanaugh, J.S. Smolen.** Possible discontinuation of therapies in rheumatic diseases – as with initiation of therapies, a shared decision between patient and rheumatologist. *Clin Exp Rheumatol.* 2013 Jul-Aug; 31(4 Suppl 78):S1-3.
2. **Wallace C.A., Giannini E.H., Huang B. et al.** American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res* (Hoboken). 2011 Jul; 63(7):929-36.
3. **A. Ravelli, A. Martini.** Remission in Juvenile Idiopathic Arthritis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43).
4. **Consolaro A., Bracciolini G., Ruperto N.** Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum.* 2012 Jul; 64(7):2366-74.
5. **Smolen J.S., Aletaha D., Bijlsma J.W. et al.** Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
6. **S. Verazza, G. Negro, D. Marafon, et al.** Possible discontinuation of therapies after clinical remission in juvenile idiopathic arthritis. *Clin Exp Rheumatol.* 2013 Jul-Aug; 31(4 Suppl 78):S98-101; S102-7.
7. **Otten M.H., Prince F.H., Armbrust W., et al.** Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. *JAMA.* 2011 Dec 7; 306(21):2340-7.
8. **Papsdorf V., Horneff G.** Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis. *Rheumatology* 2011; 50:214-221
9. **Solari N., Palmisani E., Consolaro A. et al.** Factors Associated with Achievement of Inactive Disease in Children with Juvenile Idiopathic Arthritis Treated with Etanercept *J Rheumatol.* 2013 Feb; 40(2):192-200.
10. **Trachana M., Pratsidou-Gertsi P., Badouraki M. et al.** Achievement of clinical remission in patients with juvenile idiopathic arthritis under a 2-10-year Etanercept exposure. *Clin Rheumatol.* 2013 Aug; 32(8):1191-7.
11. **Prince F.H., Twilt M., Simon S.C. et al.** When and how to stop etanercept after successful treatment of patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2009; 68:1228-9.
12. **Remesal A. de l.J., Merino R., Garcia-Consuegra J.** Discontinuation of etanercept after successful treatment in patients with juvenile idiopathic arthritis. *J Rheumatol* 2010; 37: 1970-1.
13. **Pratsidou-Gertsi P., Trachana M., Pardalos G. et al.** A follow-up study of patients with juvenile idiopathic arthritis who discontinued etanercept due to disease remission. *Clin Exp Rheumatol* 2010; 28: 919-22.
14. **Postepski J., Kobusinska K., Olesinska E. et al.** Clinical remission in juvenile idiopathic arthritis after termination of etanercept. *Rheumatol Int* 2012 July 21.
15. **Baszis K., Garbutt J., Toib D. et al.** Clinical outcomes after withdrawal of anti-tumor necrosis factor alpha therapy in patients with juvenile idiopathic arthritis: a twelve-year experience. *Arthritis Rheum* 2011; 63:3163-8.
16. **Cai Y., Liu X., Zhang W. et al.** Clinical trial of etanercept tapering in juvenile idiopathic arthritis during remission. *Rheumatol Int.* 2013 Sep; 33(9):2277-82
17. **Southwood T.R., Foster H.E., Davidson J.E. et al.** Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. *Rheumatology* (Oxford),Vol. 50, Issue 1, 2010:189-195
18. **Foell D., Wulffraat N., Wedderburn L.R. et al.** Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 2010; 303:1266-73.
19. **Moncrieffe H., Ursu S., Holzinger D. et al.** A subgroup of juvenile idiopathic arthritis patients who respond well to methotrexate are identified by the serum biomarker MRP8/14 protein. *Rheumatology* (Oxford). 2013 Apr 25
20. **Magni-Manzoni S., Scire C.A., 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; 72:223-228
21. **Wakefield R.J., D'Agostino M.A., Naredo E. et al.** After treat-to-target: can a targeted ultrasound initiative improve RA outcomes. *Ann Rheum Dis* 2012; 71:799-803
22. **Scire C.A., Montecucco C., Codullo V. et al.** Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatology* (Oxford) 2009; 48: 1092-7.
23. **Kawashiri S., Suzuki T., Nakashima Y. et al.** Ultrasonographic examination of rheumatoid arthritis patients who are free of physical synovitis: power Doppler subclinical synovitis is associated with bone erosion. *Rheumatology* (Oxford), Dec. 5, 2013 doi:10.1093/rheumatology/ket405
24. **Magni-Manzoni S., Scire C.A., 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.
25. **Lanni S., Wood M., Ravelli A., Magni Manzoni S., Emery P., Wakefield R.J.** Towards a role of ultrasound in children with juvenile idiopathic arthritis. *Rheumatology* (Oxford). 2013 Mar; 52(3):413-20. doi: 10.1093/rheumatology/ kes287. Epub 2012 Nov 11.
26. **Collado Ramos P.** Ultrasound imaging in juvenile idiopathic arthritis for the rheumatologist. *Clin Exp Rheumatol.* 2014 Feb 17.
27. **Brown A., Hirsch R., Laor T. et al.** Do patients with juvenile idiopathic arthritis in clinical remission have evidence of persistent inflammation on 3T magnetic resonance imaging? *Arthritis Care Res* 2012; 64: 1846-54
28. **Magni-Manzoni S., Malattia C., Lanni S., Ravelli A.** Advances and challenges in imaging in juvenile idiopathic arthritis. *Nat Rev Rheumatol.* 2012 Mar 27; 8(6): 329-36.
29. **Kavanaugh A., Smolen J.S.** The when and how of biologic agent withdrawal in rheumatoid arthritis: learning from large randomised controlled trials. *Clin Exp Rheumatol* 2013; 31 (Suppl. 78): S19-S21.
30. **Tanaka Y., Hirata S., Saleem B., Emery P.** Discontinuation of biologics in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2013; 31 (Suppl. 78): S22-S27.
31. **van den Broek M., Lems W.F., Allaart C.F.** Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis? *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S2