Possible discontinuation of therapies after clinical remission in juvenile idiopathic arthritis

S. Verazza¹, G. Negro¹, D. Marafon¹, A. Consolaro¹, A. Martini¹², A. Ravelli²

¹Istituto Giannina Gaslini, Genova, Italy; ²University of Genova, Genova, Italy.
Sara Verazza, MD
Giorgia Negro, MD
Denise Marafon, MD
Alessandro Consolaro, MD, PhD
Alberto Martini, MD
Angelo Ravelli, MD
Please address correspondence to:
Angelo Ravelli, MD
Pediatria II, Istituto G. Gaslini,
Largo G. Gaslini 5,
16147 Genova, Italy.
E-mail: angeloravelli@ospedale-gaslini.ge.it
Received on August 16, 2013; accepted in revised form on August 26, 2013.
© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2013.

Key words: juvenile idiopathic arthritis, remission, inactive disease, treatment discontinuation, medication withdrawal

ABSTRACT

Several studies have examined effects of discontinuing treatment after clinical remission in children with JIA. So far, only methotrexate and tumour necrosis factor α (TNF) inhibitors have been investigated. Overall, the relapse rate after termination of these medications was substantial. However, with the exception of one controlled trial of methotrexate, all analyses are retrospective. In addition, the results obtained for TNF-α inhibitors are variable and conclusions of existing studies are often divergent. No consistent predictors of the risk of flare were identified. Some evidence exists that low doses of medications may be sufficient to maintain remission. Because achievement of inactive disease has become increasingly more common in paediatric rheumatology practice, evidence-based data and expert recommendations to guide drug discontinuation are needed. This information should help to avoid both the risks and costs of prolonged therapy and to minimise the likelihood of disease flares. It should also be clarified whether it is more advantageous to stop treatment abruptly or to taper it gradually by reducing the dosage progressively or by increasing the interval between doses. Another key objective for future studies is to identify predictors of disease flare after treatment discontinuation. In addition, the optimal policy for discontinuation of other biologic medications used in children with JIA, such as anakinra, abatacept, tocilizumab, and canakinumab, should be established.

Introduction

Recent therapeutic advances have increased considerably the potential of achieving disease remission in children with juvenile idiopathic arthritis (JIA) (1). Data obtained in clinical trials, national registries and single-centre series on biologic medications over the last 5 years document a substantial rate of inactive disease (2-7) (Table I). 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. However, currently no guidelines or recommendations are available concerning appropriate discontinuation of medications after attainment of inactive disease status. As a result, treatment practices vary widely and remain empiric and physician-dependent.

Several studies have examined the effect of discontinuing treatment in children with JIA who had achieved a state of clinical remission. Most of these analyses have focused on methotrexate and tumour necrosis factor α (TNF-α) inhibitors, which are currently the anti-rheumatic medications most frequently used in children with chronic arthritis.

Discontinuation of methotrexate

In studies published before the 2000s, reported rates of remission in JIA patients treated with methotrexate varied from 6.9% to 45%; the average duration of treatment until remission was around 1 year (8). Due to the concerns from the earlier methotrexate era about the risk of long-term liver toxicity, in the past methotrexate was often discontinued shortly after complete disease control was achieved. However, a high frequency of relapse after methotrexate withdrawal was reported (9-11). Based on these findings, most investigators favored continuing methotrexate therapy longer after clinical remission was attained. However, at that time there was no evidence-based information to help in clinical decision-making regarding the length of methotrexate treatment after remission. Furthermore, it was not established whether the dosage and frequency of administration

Competing interests: none declared.

S-98
should remain stable or be decreased gradually. Investigation of these issues at that time was hampered by the lack of a widely accepted definition for remission in JIA. The first standardised criteria for inactive disease and clinical remission in JIA were developed in the early 2000s (12).

A retrospective analysis performed in 2004 found no difference in the relapse rate between patients who were discontinued from methotrexate treatment early (after a mean of 3.8 months) or late (after a mean of 12.6 months) after the documentation of disease remission (13). This observation was confirmed in a subsequent multicentre, medication-withdrawal randomised clinical trial, which showed that a 12-month vs. 6-month withdrawal of MTX did not reduce the relapse rate in patients with JIA in remission (14). The frequency of flare within 1 year among the 297 patients who stopped therapy while in remission was 39.6% and 39.5% among patients who were discontinued after 6 and 12 months, respectively. Altogether, these findings suggested that longer continuation of methotrexate after the achievement of remission did not reduce the risk of flare after treatment discontinuation. However, because in the randomised trial the likelihood of flare was assessed within 1 year after MTX withdrawal and follow-up times beyond 1 year were overall shorter in the 12-month group than in the 6-month group, the effect on prevention of later flares could not be established.

**Discontinuation of TNF-α inhibitors**

The clinical outcomes after withdrawal of TNF-α inhibitors have been evaluated only in retrospective studies. Prince and co-workers (15) described 19 children in whom etanercept was discontinued 0 to 4.7 years after the attainment of inactive disease. Ten patients (53%) had sustained disease quiescence for a median of 0.8 years. These patients had taken the medication longer and had a longer period of clinical remission on medication (1.5 vs. 0 years) than did the 9 patients who experienced a disease flare. Based on these findings, the authors suggested that patients with JIA should meet the criteria for clinical remission on medication for at least 1.5 years before consideration of discontinuation of etanercept, and that etanercept should be withdrawn gradually. Remesal et al. (16) reported 26 children whose etanercept therapy was discontinued following disease remission. The mean duration of etanercept therapy was 19 months, and treatment was continued for a mean of 14.7 months after achievement of inactive disease. Drug withdrawal was abrupt in 14 patients, and gradual in 12 other patients either by reducing the dose or by increasing the interval between doses. After cessation of etanercept administration, 69% of patients relapsed after a mean 5.8 months. Survival curve analysis showed that the cumulative probability of remaining symptom-free was 50% at 6 months and 39% at 12 months. 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. Owing to the observation that the 12 patients in whom the medication was reduced gradually did not relapse until complete termination, the authors speculated that low doses of etanercept may be sufficient to maintain remission.

Pratsidou-Gertsi et al. (17) described the disease course of 11 patients who were followed up for 12.2 to 27 months after etanercept withdrawal. The median treatment duration was 36 months. The medication was discontinued abruptly in 9 of the 11 patients, and tapered gradually by spacing the administration further apart over a 3-month period in the remaining 2 patients. All patients flared 1 to 15 months (median 3 months) after discontinuation of etanercept. Time to flare was not related either to the disease course (polyarticular or oligoarticular) or the method of drug discontinuation (abruptly or tapering). The level of disease activity, as measured with the Juvenile Arthritis Disease Activity Score (JADAS) (18), was found to be lower during disease flares than at the time of etanercept initiation.

Data of 39 patients followed in 2 Polish paediatric rheumatology centres who were discontinued from etanercept because of disease remission were reported by Postepski et al. (19). The mean duration of therapy with etanercept was 34.7 months, the mean duration of remission on medication before withdrawal of etanercept was 21.3 months, and the mean duration of remission after etanercept discontinuation was 14.2 months. Only 30.8% of patients did not develop a disease exacerbation until the end of follow-up at a mean of 25.4±12 (range 16–60) months. Early disease flares (i.e. flares within 6 months after treatment cessation) were observed in 38.5% of patients. No predictor of disease course after treatment discontinuation was identified. The conclusion of these authors was that a subset of patients with high risk of disease relapse might deserve a longer etanercept administration to maintain remission.

The largest study performed so far is that of Baszis et al. (20), who retrospectively reviewed clinical data of 171 patients who underwent 255 discrete episodes of treatment with TNF-α blockers over a 12-year period. Of the 136 patients with inactive disease at the time of termination of anti-TNF-α therapy, 25% experienced a disease flare within 1 year after stopping treatment. These findings suggest that continuation of etanercept should be withdrawn gradually.

### Table I. Frequency of inactive disease in clinical trials, national registries and single-centre series on biologic medications.

<table>
<thead>
<tr>
<th>First author, year, reference number</th>
<th>Medication</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Inactive disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruperto, 2008 (2)</td>
<td>Abatacept</td>
<td>Clinical trial</td>
<td>190</td>
<td>30*</td>
</tr>
<tr>
<td>De Benedetti, 2012 (3)</td>
<td>Tocilizumab</td>
<td>Clinical trial</td>
<td>112</td>
<td>28**</td>
</tr>
<tr>
<td>Ruperto, 2012 (4)</td>
<td>Canakinumab</td>
<td>Clinical trial</td>
<td>176</td>
<td>31*</td>
</tr>
<tr>
<td>Otten, 2011 (5)</td>
<td>Etanercept</td>
<td>National registry</td>
<td>262</td>
<td>37–49</td>
</tr>
<tr>
<td>Papsdorf, 2011 (6)</td>
<td>Etanercept</td>
<td>National registry</td>
<td>787</td>
<td>47.6</td>
</tr>
<tr>
<td>Solari, 2013 (7)</td>
<td>Etanercept</td>
<td>Single-centre series</td>
<td>173</td>
<td>50.3</td>
</tr>
</tbody>
</table>

*Only patients with systemic arthritis; **Among the 60 patients who were given abatacept in the double-blind phase; End of open-label extension phase; End of open-label phase of trial 2.
flare within 3 months, and 25% more between 3 and 6 months, while 50% had inactive disease sustained for 6 months. Thirty-two percent of the patients achieved clinical remission (12 months of inactive disease) without anti-TNF-α therapy. The duration of inactive disease ranged from 0.2 to 42.1 months (median 4.2 months). TNF-α antagonists were withdrawn a median of 6.1 months after inactive disease was reached. No significant association was observed between the time to disease flare after treatment discontinuation and the length of time from the diagnosis of JIA to the initiation of anti-TNF-α therapy, the duration of therapy following the onset of inactive disease, or the total duration of treatment with treatment with TNF-α antagonists prior to discontinuation. The category of JIA, sex, and age at diagnosis were not associated with the risk of relapse. The results of the study led the authors to suggest that prolonged treatment with TNF-α antagonists does not increase the likelihood of sustained remission after withdrawal of therapy.

### Can disease course after treatment discontinuation be predicted?

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. The search for demographic or clinical predictors in the studies performed thus far concerning either methotrexate or TNF-α antagonists has provided inconsistent or conflicting results. Better insights into this issue may be obtained through improvement of the standardisation of study design and predictor variables and the inclusion of well established quantitative clinical measures, including the Wallace criteria for inactive disease and clinical remission (12, 21) and the JADAS (18).

It has been argued that remission defined by the current clinical criteria (12, 21) may not equate to “immunological” remission and that immunological biomarkers may detect subclinical inflammation in patients with clinical remission that would exclude immunological remission (14). Recent studies have shown that the levels of myeloid-related proteins 8 and 14 (MRP8/14), which are secreted by activated phagocytes, reflect subclinical inflammation that may affect the risk for disease flares (22, 23). In the above mentioned controlled trial of methotrexate withdrawal, higher MRP8/14 concentrations were associated with risk of relapse after treatment discontinuation (14). This observation led to hypothesis that increased serum concentration of MRP8/14 can identify patients with unstable remission who are at increased risk of relapse, and that assessment of these proteins may support a decision to discontinue the medication. The utility of these biomarkers merits further exploration in larger patient samples and in the real world of daily clinical practice.

In adult patients with rheumatoid arthritis, there is evidence that synovitis detected by imaging may be frequent in patients who meet clinically-defined remission criteria (24). Furthermore, vascularisation detected by power Doppler ultrasound was found to predict short-term disease flare after clinical remission (25, 26). The presence of ongoing synovial pathology in one or more joints was also observed in a sizable proportion of JIA patients classified as having inactive disease on clinical grounds (27-29). However, the clinical significance and prognostic value of these findings is unclear, as the presence of abnormalities on ultrasound, including power Doppler signal, did not predict subsequent synovitis flare (28).

The lack of predictive value of power Doppler signal in JIA has been related to the difficulty to establish whether the presence of juxta-articular flow at power Doppler examination in the growing child represents normal flow of the well vascularised cartilage of the epiphysis or synovial hyperemia indicating inflammation. Another possible explanation lies in the potential confounding influence of the physiologically enhanced synovial blood flow on the appraisal of low-grade power Doppler signal in growing children (28, 30, 31). This finding suggests that residual synovitis on imaging should not affect clinical decisions and, in particular, should not indicate treatment in the absence of clinical indications. However, more data are needed to establish the value of imaging in the definition of remission in children with JIA.

### Conclusion

In recent years, several studies have addressed the issue of treatment discontinuation after achievement of clinical remission in children with JIA. Overall, the relapse rate after termination of both methotrexate and TNF-α antagonists was substantial. However, no consistent predictors of the risk of flare were identified.

A problem with existing studies is that, with the exception of the controlled trial of Foell et al. concerning methotrexate (14), all analyses were retrospective. Regarding TNF-α inhibitors, there is a wide disparity in the results obtained, and the conclusions or recommendations provided by the authors are often divergent. Another shortcoming is that only methotrexate and anti-TNF-α medications have been investigated, and no information is available for other biologic medications used in children with JIA, such as anakinra, abatacept, tocilizumab, and canakinumab. The lack of evidence-based data from clinical trials and clinical care, and guidelines to aid in the withdrawal of medications after disease remission, contrasts with the availability of well-established recommendations for the initiation and safety monitoring of therapeutic agents in JIA (32). Since inactive disease is now achieved with increasing frequency in children with JIA, there appears an urgent need for randomised controlled trials, analyses of clinical databases, and expert recommendations to guide discontinuation.

Both the optimal timeline for withdrawal after documentation of inactive disease and the modality of discontinuation are of foremost importance. It should be established whether greater advantage maybe be seen when treatment is discontinued abruptly, or when tapered gradually by reducing the dosage progressively or by increasing the
interval between doses. A specific issue in patients who are taking methotrexate and biologic medications simultaneously is to ascertain which medication should be discontinued first.

Another important matter for future studies is to identify predictors of disease flare after treatment discontinuation. Immunologic biomarkers, particularly the myeloid-related proteins MRPs8/14, appear more promising than demographic and clinical parameters and ultrasound. However, well-designed prospective studies must be conducted to recognize all potential predictors.

References


