Treatment withdrawal following remission in juvenile idiopathic arthritis: a systematic review of the literature

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Table S1. Assessment of quality of evidence in regard to medication withdrawal in remission of JIA: observational papers on methotrexate

	Klotsche, 2018 [1]	Gottlieb, 1997 [2]	Ravelli, 1995 [3]
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	CD	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	Y	Y	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	N	N
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	N	Y	Y
10. Was the exposure(s) assessed more than once over time?	Y	Y	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	N	N
12. Were the outcome assessors blinded to the exposure status of participants?	N	N	N
13. Was loss to follow-up after baseline 20% or less?	N	Y	Y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	N	N
Quality rating: good, fair, or poor?	Fair	Poor	Poor
Explanation of poor rating		Heterogeneous population, limited consideration of confounders	Small sample, unclear validity of outcome, limited consideration of confounders

CD cannot determine, N no, Y yes

Table S2. Assessment of quality of evidence in regard to medication withdrawal in remission of JIA: randomized trials on methotrexate

	Foell, 2010 [4]
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Y
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Y
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	N
4. Were study participants and providers blinded to treatment group assignment?	N
5. Were the people assessing the outcomes blinded to the participants' group assignments?	N
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Y
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Y
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Y
9. Was there high adherence to the intervention protocols for each treatment group?	N
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Y
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Y
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Y
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Y
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Y
Quality rating: good, fair, or poor?	Fair
Explanation of poor rating	

N no, Y yes

Table S3. Assessment of quality of evidence in regard to medication withdrawal in remission of JIA[1]: observational papers on biologics[2]

	Minden, 2019 [5]	Ter Haar, 2019 [6]	Aquilani, 2018 [7]	Lovell, 2018 [8]	Ruperto, 2018 [9]	Simonini, 2018 [10]	Su, 2017 [11]	Iglesias, 2014 [12]	Cai, 2013 [13]	Postepski, 2013 [14]	Baszis, 2011 [15]	Otten, 2011 [16]	Pratsidou-Gertsi, 2010 [17]	Remesal, 2010 [18]	Prince, 2009 [19]
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	NA	Y	NA	Y	Y	Y	Y	NA	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	CD	Y	Y	Y	NA	Y	CD	Y	CD	CD	Y	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	N	Y	N	N	Y	CD	CD	Y	Y	CD	Y	Y	Y	N	N
5. Was a sample size justification, power description, or variance and effect estimates provided?	Y	N	Y	Y	NA	Y	Y	N	N	N	Y	NA	N	Y	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CD	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	NA	Y	Y	NA	Y	Y	N	Y	Y	Y	Y	N	Y	Y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	N	N	Y	N
12. Were the outcome assessors blinded to the exposure status of participants?	N	N	N	N	NA	N	N	N	N	N	N	N	N	N	N
13. Was loss to follow-up after baseline 20% or less?	Y	Y	CD	N	Y	CD	CD	CD	Y	CD	CD	CD	CD	CD	CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N	Y	Y	Y	NA	N	N	N	N	N	N	NA	N	N	N

Quality rating: good, fair, or poor?	Fair	Fair	Fair	Fair	Fair	Fair	Poor	Poor	Fair	Poor	Fair	Fair	Poor	Poor	Poor
Explanation of poor rating							Unclear composition of comparison groups, unclear if inclusion criteria uniformly applied, limited consideration of confounders	Small sample, unclear validity of outcome		Small sample, unclear validity of outcome, unclear time period of study			Small sample, limited validity of exposures and outcomes	Selection bias (did not include those who tapered but did not stop), small sample	Selection bias (did not include those who tapered but did not stop), small sample

CD cannot determine, N no, NA not applicable, Y yes

[1] Studies that did not primarily focus on treatment withdrawal were evaluated with respect to the content on treatment withdrawal

[2] Observational studies included randomized trials that did not primarily focus on treatment withdrawal

Table S4. Assessment of quality of evidence in regard to medication withdrawal in remission of JIA[1]: observational papers on combination treatment[2]

	Hissink Muller, 2018 [20]	Guzman, 2016 [21]	Chang, 2015 [22]	Wallace, 2014 [23]
1. Was the research question or objective in this paper clearly stated?	NA	Y	Y	NA
2. Was the study population clearly specified and defined?	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	N	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	NA	Y	N	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	N	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	Y	Y	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	NA
10. Was the exposure(s) assessed more than once over time?	N	N	N	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	Y	N	N	NA
13. Was loss to follow-up after baseline 20% or less?	Y	Y	N	N
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NA	Y	N	N
Quality rating: good, fair, or poor?	Fair	Good	Fair	Fair
Explanation of poor rating				

N no, NA not applicable, Y yes

[1] Studies that did not primarily focus on treatment withdrawal were evaluated with respect to the content on treatment withdrawal

[2] Observational studies included randomized trials that did not primarily focus on treatment withdrawal

Table S5. Assessment of quality of evidence in regard to medication withdrawal in remission of JIA[1]: observational papers on uveitis

	Acharya, 2018 [24]	Breitbach, 2017 [25]	Simonini, 2017 [26]	Lerman, 2015 [27]	Shakoor, 2014 [28]	Saboo, 2013 [29]	Kalinina Ayuso, 2011 [30]
1. Was the research question or objective in this paper clearly stated?	Y	NA	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	CD	Y	Y	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	N	Y	N	Y	N	N	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	Y	N	Y	Y	Y	Y	Y
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	NA	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	NA	Y	Y	Y	Y	Y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	NA	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	N	NA	N	N	N	N	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	N	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	N	N	N	N	N	N	N
13. Was loss to follow-up after baseline 20% or less?	CD	CD	CD	CD	CD	N	CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N	NA	N	NA	N	N	N
Quality rating: good, fair, or poor?	Poor	Fair	Fair	Fair	Poor	Poor	Fair
Explanation of poor rating	Small sample; long study period with incomplete adjustment for changes in clinical practice; overfit models without disease severity		Selection bias (inclusion only of peple who stopped, requirement for ≥6 months f/u off treatment)		Very heterogeneous population, small sample (4) with JIA, limited consideration of disease severity	Small sample, long study period with incomplete adjustment for changes in clinical practice, limited adjustment for confounding	

CD cannot determine, N no, NA not applicable, Y yes

[1] Studies that did not primarily focus on treatment withdrawal were evaluated with respect to the content on treatment withdrawal

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