1. Introduction

Immunosuppressive agents are drugs that inhibit or prevent activation of the immune system. They are commonly prescribed to prevent rejection of transplanted organs or for the treatment of inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease. Some observational studies indicate that the immunosuppressive effect of the drugs could lead to impaired wound healing and an increased risk of infection in patients treated with these agents. Conversely, the discontinuation of immunosuppressive treatment could induce flares of disease activity and long-term interruptions of therapy could induce the formation of anti-drug-antibodies and subsequently decrease the effect of immunosuppressives.

At present, the guideline for the prevention of surgical site infection (SSI) published by the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) is the only one that has issued a recommendation regarding the administration of immunosuppressive agents in the perioperative period. This guideline recommends avoiding the use of immunosuppressive agents in the perioperative period, if possible. However, this recommendation is not based upon systematic reviews of the literature and meta-analyses or a rigorous evaluation of the quality of the available evidence. Of note, several other SSI prevention guidelines do not address this topic.

The purpose of this systematic review is to evaluate the influence of immunosuppressive agents on the incidence of SSI and to determine whether the discontinuation compared to the continuation of immunosuppressive medication in the perioperative period is effective to prevent SSI.

2. PICO question

Should immunosuppressive agents be discontinued perioperatively and does this affect the incidence of SSI?

- Population: patients of any age taking immunosuppressive agents and undergoing surgical procedures
- Intervention: discontinuation of immunosuppressive agents
- Comparator: continuation of immunosuppressive agents
- Outcomes: SSI, SSI-attributable mortality
3. Methods

The following databases were searched: Medline (via Ovid); Excerpta Medica Database (EMBASE via Ovid); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 17 January 2014. Language was restricted to English, French and Spanish. A comprehensive list of search terms was used (Appendix 1).

Two independent authors screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and then reviewed independently by two authors for eligibility based on inclusion criteria. Duplicate studies were excluded.

The two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled trials (RCTs) (Appendix 3a) and the Newcastle-Ottawa Quality Assessment Scale for cohort studies (Appendix 3b). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 as appropriate (Appendix 4). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software) was used to assess the quality of the body of retrieved evidence (Appendix 5).
4. Study selection

Flow chart of the study selection process

Potentially relevant articles $n = 275$
- Medline (via Ovid) $n = 45$
- EMBASE $n = 106$
- CINAHL $n = 51$
- Cochrane CENTRAL $n = 22$
- WHO Global Library $n = 51$

Citations identified through other sources $n = 13$

Total articles after removal of duplicates $n = 270$

Total articles screened $n = 270$

Excluded after title and abstract screening $n = 232$

Full-text articles assessed for eligibility $n = 38$

Full-text articles excluded $n = 30$
- Not relevant $n = 18$
- Review/editorial $n = 6$
- No full text available $n = 8$

One randomized controlled trial, one quasi-randomized and 6 observational studies included in the analysis $n = 8$
5. **Summary of the findings and quality of the evidence**

Eight studies comparing perioperative discontinuation vs. continuation of immunosuppressive medication with an SSI outcome were identified, including one randomized controlled trial (RCT)\(^9\), one quasi-RCT\(^10\) and 6 observational studies\(^1,11-15\). Included patients were taking immunosuppressive agents and undergoing mainly orthopaedic procedures\(^1,9,12,14,15\), but also abdominal\(^13\) and hand\(^1\) surgery. The underlying disorder of most patients was rheumatoid arthritis, but also Crohn’s disease\(^13\) and other inflammatory rheumatic diseases\(^1\). According to the different immunosuppressive agents investigated in the studies, the following comparisons were evaluated:

Discontinuation vs. continuation of:

1. methotrexate (MTX)
2. tumour necrosis factor (TNF) inhibitors (anti-TNF)

1. Six studies (one RCT\(^9\), one quasi-RCT\(^10\) and 4 observational studies\(^11-13,15\)) investigated MTX. While the quasi-RCT showed an increased risk for SSI when MTX was discontinued\(^10\), the RCT had no events estimable in either group\(^9\). One study showed a borderline, significant decreased risk for SSI when MTX was discontinued\(^11\), whereas 3 studies showed no difference\(^12,13,15\). The meta-analysis showed that the perioperative discontinuation of MTX might increase (Appendix 4, comparison 1a [RCTs]) or have no effect on the risk of SSI (Appendix 4, comparison 1b [observational studies]) when compared to continuation of MTX. The combined odds ratio [OR] was 7.75 [95% confidence interval [CI]: 1.66–36.24] for the RCTs and 0.37 [95% CI: 0.07–1.89] for the observational studies.

The quality of evidence for this comparison was very low for both the RCTs and the observational studies (Appendix 5) due to risk of bias, imprecision and indirectness for the RCTs and to imprecision for the observational studies.

2. Two observational studies\(^1,14\) investigating anti-TNF were identified. One study showed a significantly decreased risk for SSI when anti-TNF was discontinued\(^1\) and the other showed no difference in risk\(^14\). A meta-analysis of the 2 studies showed that the perioperative discontinuation of anti-TNF might decrease the risk of SSI (Appendix 4, comparison 2) when compared to the continuation of anti-TNF (OR: 0.59; 95% CI: 0.37–0.95).

The quality of the evidence for this comparison was very low due to imprecision and indirectness (Appendix 5).

The body of retrieved evidence focused mainly on adult patients and few studies included a paediatric population\(^1,13\). The literature search did not identify any studies that reported on SSI-attributable mortality.

The review identified 4 studies comparing patients with and without MTX undergoing the same type of surgery\(^10,15-17\), as well as an additional 4 studies comparing patients with and without anti-TNF medication undergoing the same type of surgery\(^14,18-20\). Furthermore, one study compared the time of discontinuation between anti-TNF
exposure and SSI and another study compared surgical patients with different medication (anti-TNF vs. disease-modifying anti-rheumatic drugs) \(^{18,21}\). After careful appraisal of this evidence, the research team and the Guidelines Development Group decided to exclude these studies as they did not meet the PICO question criteria.

In conclusion, the available evidence can be summarized as follows.

- **Perioperative discontinuation vs. continuation of MTX**
  
  Overall, a very low quality of evidence shows that the perioperative discontinuation of MTX might be harmful or has no effect on the risk of SSI when compared to the continuation of MTX.

- **Perioperative discontinuation vs. continuation of anti-TNF**
  
  Very low quality evidence shows that the perioperative discontinuation of anti-TNF might have a benefit in reducing the SSI rate when compared to the continuation of anti-TNF.

Some serious limitations can be observed within the available studies. There was a high or unclear risk of allocation concealment and outcome assessor blinding in the RCTs. Overall, the included studies cover a limited number of events and the results show very wide CIs. The population of the RCTs included only patients with rheumatoid arthritis.

6. **Other factors considered in the review of studies**

The systematic review team identified the following other factors to be considered.

*Potential harms*

Several aspects should be taken into account when deciding whether to continue or discontinue immunosuppressive therapy perioperatively. The risk associated with discontinuation, such as a flare-up of the underlying disease, should be assessed individually for each patient, involving the prescribing physician, the patient and the surgeon \(^{9,10,16-21}\). The possible side-effects of discontinuation may possibly outweigh the advantages for the reduction in SSI. In general, the risk of major adverse events associated with discontinuation is high in patients taking immunosuppressive therapy after organ transplantation or for rheumatoid arthritis, whereas the risk might be lower in those taking immunosuppressive agents for inflammatory bowel disease \(^{9,10,16-21}\).

7. **Key uncertainties and future research priorities**

The systematic review team identified the following key uncertainties and future research priorities.

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. In current studies, a significant heterogeneity exists regarding the definition used for SSI, the time between discontinuation and surgery and the dosage of the immunosuppressive therapy, thus
making it impossible to draw firm conclusions. Well-designed RCTs are needed to clarify this issue. Trials should examine also the optimal time between discontinuation of the immunosuppressive agent(s) and time of surgery. The importance of the optimal dose of the various immunosuppressive therapy agents with regards to the SSI rate should be investigated also. Importantly, studies should take into account new immunosuppressive agents as well as conventional corticosteroids. Both the effect on SSI of the discontinuation of chronically used corticosteroids and the avoidance of single perioperative high doses should be investigated. In patients taking immunosuppressive agents with inflammatory bowel disease, other endpoints might be of more relevance than SSI, such as anastomotic leakage. Additional controversy exists regarding the time needed to achieve the elimination of therapeutic concentrations of immunosuppressive agents. Some studies have suggested 4 weeks, although therapeutic concentrations persist until at least 6 weeks in general after administration of the immunosuppressive agent.
APPENDICES

Appendix 1: Search terms

**Medline (via OVID)**

1. wound infection.mp. or exp wound infection/
2. exp surgical procedures, operative/ or exp perioperative period/ or exp preoperative care/ or exp perioperative care/ or (surger* or operat* or perioperat* or peri-operat* or pre-operat* or preoperat*).ti,ab,kw.
3. exp immunosuppressive agents/ or exp adrenal cortex hormones/ or (immuno suppress* or immunosuppress* or immune suppress* or immunesuppress* or corticosteroid*).ti,ab,kw.
4. surgical wound infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
5. (discontinu* or continu*).ti,ab,kw.
6. 2 and 3 and 4 and 5
7. limit 6 to yr="1990 - 2014"
8. 1 or 4
9. 3 and 5
10. 2 and 8 and 9
11. limit 10 to yr="1990 -Current"

**EMBASE**

1. exp surgery/ or perioperative period/ or preoperative care/ or (surger* or operat* or perioperat* or peri-operat* or pre-operat* or preoperat*).ti,ab,kw.
2. immunosuppressive agent/ or corticosteroid/ or (immuno suppress* or immunosuppress* or immune suppress* or immunesuppress* or corticosteroid*).ti,ab,kw.
3. surgical infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
4. (discontinu* or continu*).ti,ab,kw.
5. 1 and 2 and 3 and 4
6. limit 5 to yr="1990 - 2014"
7. exp wound infection/
8. 3 or 7
9. 2 and 4
10. 1 and 8 and 9
11. limit 10 to yr="1990 -Current"

**CINAHL**

S1. (MH "wound infection+") OR "wound infection" OR (MH "surgical wound infection")
S2. (MH "immunosuppressive agents+") OR "immunosuppressive agents"
S3. (MH "immunosuppression+") OR "immunosuppression"
S4. S2 OR S3 S5. S1 AND S4

**Cochrane CENTRAL**

(wound infections) AND (immunosuppressive therapy)

**WHO Global Regional Medical Databases**

((ssi) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections)) AND immunosuppressive

*ti: title; ab: abstract; kw: key word*
### Appendix 2: Evidence table

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Design, scope, setting, population</th>
<th>Objective</th>
<th>SSI definition</th>
<th>Type of surgery</th>
<th>Study methods</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berthold 2013 1</td>
<td>Observational cohort study, single centre, university hospital. All rheumatic patients undergoing elective surgery</td>
<td>To assess the influence of TNF inhibitors on the risk of developing SSI.</td>
<td>CDC health care-associated SSI</td>
<td>Elective orthopaedic or hand surgery</td>
<td>Consecutive selection of patients between 2003-2009.</td>
<td>A) Discontinuation of TNF inhibitors pre-operatively. B) TNF inhibitors continued at stable dosage.</td>
<td>A) 872 procedures SSI (superficial and deep): 25/872 (3%) B) 681 procedures SSI: 35/681 (5%) AE: not specified LF: not specified P-value/OR: NS Mortality: not specified</td>
</tr>
<tr>
<td>den Broeder 2006 14</td>
<td>Observational cohort study, multicentre. All patients with rheumatoid arthritis, patients that underwent elective orthopaedic surgery</td>
<td>To assess the effect of withholding vs. maintaining anti-TNF therapy on the incidence of SSI.</td>
<td>CDC prevention criteria for postoperative infection.</td>
<td>Elective orthopaedic surgery</td>
<td>All consecutive patients with rheumatoid arthritis that underwent orthopaedic surgery between 1997-2004.</td>
<td>A) No medication B) Anti-TNF stopped prior to surgery (&gt;4 times the half-life of anti-TNF agent) C) Anti-TNF continued perioperatively</td>
<td>A) 1023 procedures SSI: 41/1023 (4%) B) 104 procedures SSI: 6/104 (6%) C) 92 procedures SSI: 8/92 (9%) AE: not specified LF: not specified OR: 1.56 (95% CI: 0.52 – 4.66)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Patients</td>
<td>Procedures</td>
<td>Complications</td>
<td>Mortality</td>
<td>AE: not specified</td>
<td>LF: not specified</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
<td>------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
</tbody>
</table>
| Bridges 1991 11              | Observational cohort study, single centre, university hospital. | All patients with MTX who underwent elective orthopaedic surgery. | To compare the surgical outcome of rheumatoid arthritis patients with MTX stopped more than 4 weeks preoperatively vs. those with MTX stopped less than 4 weeks preoperatively. | NS            | Elective orthopaedic surgery | All patients with rheumatoid arthritis between 1981-1989. | A) MTX treatment within 4 weeks of surgery  
B) MTX treatment discontinued 4 weeks before surgery or no treatment at all before surgery. | 4 deaths (range, 30-144 months after surgery)  
C) 0 (0%)  
D) 0 (0%) |
| Carpenter 1996 12            | Observational cohort, single centre. | All patients undergoing elective total joint arthroplasty. | To assess the effect of low-dose MTX on postoperative complications in rheumatoid arthritis patients. | NS            | Elective total joint arthroplasty | All patients with rheumatoid arthritis receiving MTX who were to undergo total joint arthroplasty between 1982-1991 | A) MTX withheld 1 week prior to surgery and the week of the surgery (total 2 weeks)  
B) MTX maintained throughout the perioperative period | 19 procedures:  
4 complications (5%: 2 wound infections, 2 wound dehiscence)  
34 procedures:  
0 complications  
AE: not specified  
LF: 1 patient  
P-value/OR: NS |
|                              |                               |                                                                         |                                                                           |               |                                         |                   |                   |
|                              |                               |                                                                         |                                                                           |               |                                         |                   |                   |

Page 10 of 23
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Colombel 2004 | Retrospective cohort study, single centre. | All patients who underwent abdominal surgery for Crohn’s disease; median age 40 years (range, 12-83). | MTX/azathioprine or 6-mercaptopurine continued perioperatively or MTX/azathioprine or 6-mercaptopurine discontinued within 4 weeks prior to surgery. | Septic complications: | P-value/OR: NS  
Mortality: not specified |

Septic complications are defined as wound sepsis, intra-abdominal infections and additional abdominal infections.


A) 105 procedures  
B) 165 procedures  
AE: not specified  
LF: not specified  
P-value/OR: NS  
Mortality: 0%
Grennan 2001

**Prospective randomized study, single centre.**

All patients undergoing elective orthopaedic surgery.

**To determine whether continued MTX treatment increases the risk of postoperative infections in rheumatoid arthritis patients.**

Wound morbidity (reddening of the wound, discharge), systemic infection or wound dehiscence occurring within 1 year post-surgery.

**Elective orthopaedic surgery**

All patients with rheumatoid arthritis receiving MTX and listed for elective orthopaedic surgery.

Patients were allocated by the study coordinator who attempted to match for type of surgery using block randomization.

<table>
<thead>
<tr>
<th>A) MTX continued</th>
<th>B) MTX discontinued 2 weeks before surgery until 2 weeks after surgery</th>
<th>C) Patients with rheumatoid arthritis not taking MTX.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) 88 procedures SSI: 2/88 (2%)</td>
<td>B) 72 procedures SSI: 11/72 (41%)</td>
<td>C) 228 procedures SSI: 24/228 (11%)</td>
</tr>
</tbody>
</table>

AE (flare):  
A) 0  
B) 6 (8%)  
C) 9 (4%)  

LF: not specified  
A vs. B: *P*<0.003  
B vs. C: *P*=0.026

Mortality: not specified
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Primary Purpose</th>
<th>Methodology</th>
<th>Surgical Procedures</th>
<th>MTX Continuation</th>
<th>SSI Rate</th>
<th>AE Rate</th>
<th>LF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Retrospective cohort study, single centre. Rheumatoid arthritis patients undergoing elective orthopaedic surgery.</td>
<td>To determine the effects of the perioperative use of MTX on complications after surgery.</td>
<td>Elective orthopaedic surgery</td>
<td>All patients that underwent orthopaedic surgery between 2000-2003.</td>
<td>A) Continuation of MTX B) Discontinuation of MTX (&gt;1 week perioperatively) C) No MTX treatment</td>
<td>A) 77 procedures SSI: 3/77 (3.9%) B) 21 procedures SSI: 1/21 (4.8%) C) 103 procedures SSI: 4/103 (3.9%)</td>
<td>AE: (flares) A) 3/77 (3.9%) B) 3/21 (14.3%) C) 7/103 (6.8%) LF: not specified</td>
<td>P= NS</td>
<td>Mortality: not specified</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Prospective randomized study, single centre. Rheumatoid arthritis patients undergoing orthopaedic surgery</td>
<td>To evaluate the influence of MTX on the frequency of postoperative complications in rheumatoid arthritis patients.</td>
<td>Orthopaedic surgery</td>
<td>Consecutive patients with rheumatoid arthritis undergoing orthopaedic surgery between 1987-1990.</td>
<td>A) MTX discontinued 7 days before surgery B) MTX continued</td>
<td>A) 50 procedures SSI: 0/50 (0%) B) 39 procedures SSI: 0/39 (0%) AE: (flare) A) 1/39 B) 0/39 LF: not mentioned</td>
<td>P-value/OR: NS</td>
<td>Mortality: not specified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SSI: surgical site infection; TNF: tumor necrosis factor; CDC: Centers for Disease Prevention and Control; AE: adverse event; LF: lost to follow-up; NS: not significant; MTX: methotrexate; OR: odds ratio; CI: confidence interval
Appendix 3. Risk of bias assessment of the included studies

Appendix 3a: Studies related to discontinuation vs. continuation of immunosuppressive agents (Cochrane Collaboration tool)

<table>
<thead>
<tr>
<th>RCTs: author, year, reference</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Participants blinded</th>
<th>Care providers blinded</th>
<th>Outcome assessors blinded</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grennan, 2001* 10</td>
<td>HIGH</td>
<td>HIGH</td>
<td>HIGH</td>
<td>HIGH</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>-</td>
</tr>
<tr>
<td>Sany, 1992 9</td>
<td>HIGH</td>
<td>HIGH</td>
<td>HIGH</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>-</td>
</tr>
</tbody>
</table>

*quasi-randomized trial
RCT: randomized controlled trial
### Appendix 3b: Risk of bias assessment of studies related to discontinuation vs. continuation of immunosuppressive agents (Newcastle-Ottawa Quality Assessment Scale)

<table>
<thead>
<tr>
<th>Other controlled studies: author, year, reference</th>
<th>Representativeness of cohort</th>
<th>Selection of non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at the start</th>
<th>Comparability of cohorts</th>
<th>Assessment of outcome</th>
<th>Follow-up long enough</th>
<th>Adequacy of follow-up of cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berthold, 2013</td>
<td>B (*)</td>
<td>B</td>
<td>A (*)</td>
<td>B</td>
<td>A (*)</td>
<td>B (*)</td>
<td>A (*)</td>
<td>B (*)</td>
</tr>
<tr>
<td>den Broeder 2006</td>
<td>B (*)</td>
<td>A(*)</td>
<td>A(*)</td>
<td>B</td>
<td>A (*)</td>
<td>B (*)</td>
<td>A (*)</td>
<td>D</td>
</tr>
<tr>
<td>Bridges 1991</td>
<td>B (*)</td>
<td>A(*)</td>
<td>A(*)</td>
<td>B</td>
<td>A (*)</td>
<td>B (*)</td>
<td>A(*)</td>
<td>D</td>
</tr>
<tr>
<td>Carpenter 1996</td>
<td>B (*)</td>
<td>A(*)</td>
<td>A(*)</td>
<td>B</td>
<td>A (*)</td>
<td>B (*)</td>
<td>B</td>
<td>D</td>
</tr>
<tr>
<td>Colombel 2004</td>
<td>B (*)</td>
<td>A(*)</td>
<td>A(*)</td>
<td>B</td>
<td>A (*)</td>
<td>B (*)</td>
<td>A(*)</td>
<td>D</td>
</tr>
<tr>
<td>Murata 2006</td>
<td>A(*)</td>
<td>B</td>
<td>A(*)</td>
<td>B</td>
<td>A(*)</td>
<td>B (*)</td>
<td>A (*)</td>
<td>D</td>
</tr>
</tbody>
</table>
Appendix 4: Comparisons

Comparison 1a: Discontinuation vs. continuation of MTX (controlled trials)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>discontinuation</th>
<th>Total</th>
<th>continuation</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crenn 2001</td>
<td>11</td>
<td>72</td>
<td>2</td>
<td>88</td>
<td>100.0%</td>
<td>7.75 [1.66, 36.24]</td>
</tr>
<tr>
<td>Sary 1992</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>39</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>122</td>
<td>127</td>
<td>100.0%</td>
<td></td>
<td>7.75 [1.66, 36.24]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 11
Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.009)

MTX: methotrexate; M-H: Mantel-Haenszel (test), CI: confidence interval

Funnel plot 1a: Discontinuation vs. continuation of MTX (controlled trials)
Comparison 1b: Discontinuation vs. continuation of MTX (observational studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>discontinuation Events</th>
<th>Total</th>
<th>continuation Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridges 1991</td>
<td>0</td>
<td>24</td>
<td>4</td>
<td>19</td>
<td>17.8%</td>
<td>0.05 [0.00, 0.99]</td>
</tr>
<tr>
<td>Carpenter 1996</td>
<td>0</td>
<td>26</td>
<td>4</td>
<td>16</td>
<td>17.7%</td>
<td>0.05 [0.00, 1.05]</td>
</tr>
<tr>
<td>Colombel 2004</td>
<td>32</td>
<td>165</td>
<td>20</td>
<td>105</td>
<td>41.1%</td>
<td>1.02 [0.55, 1.90]</td>
</tr>
<tr>
<td>Murata 2006</td>
<td>1</td>
<td>21</td>
<td>3</td>
<td>77</td>
<td>23.3%</td>
<td>1.23 [0.12, 12.51]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>246</td>
<td></td>
<td>217</td>
<td>100.0%</td>
<td>0.37 [0.07, 1.89]</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td>333</td>
<td></td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $T^2 = 1.60$; $Q(3) = 7.57$, $p = 0.06$; $I^2 = 50$
Test for overall effect: $Z = 1.20$ ($p = 0.23$)

MTX: methotrexate; M–H: Mantel-Haenszel (test), CI: confidence interval

Funnel plot 1b: Discontinuation vs. continuation of MTX (observational studies)
Comparison 2: Discontinuation vs. continuation of anti-TNF (observational studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>discontinuation Events</th>
<th>Total</th>
<th>continuation Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergholdt 2013</td>
<td>25</td>
<td>872</td>
<td>25</td>
<td>631</td>
<td>83.3%</td>
<td>0.54 [0.32, 0.92]</td>
</tr>
<tr>
<td>Den Broeder 2006</td>
<td>45</td>
<td>104</td>
<td>6</td>
<td>92</td>
<td>16.7%</td>
<td>0.88 [0.27, 2.82]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>976</td>
<td>773</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.59 [0.37, 0.95]</td>
</tr>
</tbody>
</table>

Total events: 31 vs. 41
Heterogeneity: $\tau^2 = 0.00, \chi^2 = 0.53, df = 1 (P = 0.47), I^2 = 0$
Test for overall effect: $Z = 2.17 (P = 0.03)$

MTX: methotrexate; M–H: Mantel-Haenszel (test), CI: confidence interval

Funnel plot 2: Discontinuation vs. continuation of anti-TNF (observational studies)
Appendix 5: Grade tables

Comparison 1: Discontinuation vs. continuation of MTX

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>RCTs</td>
<td>serious¹</td>
<td>not serious</td>
<td>serious²</td>
<td>serious³</td>
<td>none</td>
<td>11/122 (9.0%)</td>
<td>OR 7.75</td>
<td>⬤◯◯◯</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/127 (1.6%)</td>
<td></td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
<td>none</td>
<td>33/246 (13.4%)</td>
<td>OR 0.37</td>
<td>⬤◯◯◯</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31/217 (14.3%)</td>
<td></td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

1. Risk of selection bias and detection bias
2. Patients with rheumatoid arthritis only
3. Optimal information size not met
4. Optimal information size not met and CI includes both appreciable benefit and harm (RR and RRR of 25%)

MTX: methotrexate; RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio; RR: relative risk; RRR: relative risk reduction.

Comparison 2: Discontinuation vs. continuation of anti-TNF
<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Other considerations</th>
<th>№ of patients with discontinuation of anti-TNF</th>
<th>№ of patients with continuation of anti-TNF</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Observational studies</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^1)</td>
<td>serious (^2)</td>
<td>none</td>
<td>31/976 (3.2%)</td>
<td>41/773 (5.3%)</td>
<td>OR 0.59 (0.37 to 0.95)</td>
<td>21 fewer per 1,000 (from 3 fewer to 33 fewer)</td>
</tr>
</tbody>
</table>

1. Patients undergoing orthopedic surgery only
2. Optimal information size not met

TNF: tumour necrosis factor; CI: confidence interval; OR: odds ratio
References


