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Minocycline for Relapsing-Remitting Multiple Sclerosis and Clinically Isolated Syndrome: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

AE	adverse event
CI	confidence interval
CIS	clinically isolated syndrome
CRD	University of York Centre for Reviews and Dissemination
EDSS	Expanded Disability Status Scale
EMBASE	Excerpta Medica database
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject headings
MRI	magnetic resonance imaging
MS	multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
SE	standard error

Context and Policy Issues

In 2017, there were an estimated 79,723 prevalent cases of multiple sclerosis (MS) in Canada.[1] A long-lasting yet unpredictable illness, MS is believed to involve an autoimmune reaction where the body attacks the protective myelin sheath of nerve cells in the brain and spinal cord.[2,3] Patients may experience a wide range of symptoms depending on the area of the central nervous system that is affected, including: tingling or numbing sensations, weakness, muscle spasms, urinary dysfunction, and mild cognitive impairment.[3] A first symptomatic episode, known as clinically isolated syndrome (CIS), is a potential precursor to MS.[4] Symptoms usually recede over weeks to months, yet remission may not be complete.[4] The likelihood of developing MS for patients with CIS ranges from 60% to 80%.[4] Over time a pattern of progression may emerge, such as: primary progressive, secondary progressive, progressive relapsing, and relapsing-remitting.[3] The later is an ebb and flow cycle, where flair-ups of neurological signs and symptoms are followed by a period of remission that may last months or years.[3,5]

There are no specific diagnostic tests for MS and the diagnosis is done by excluding other possible causes for the patient's signs and symptoms.[2] Several assessments may be used in the diagnosis, such as: clinical presentation, brain and spinal magnetic resonance imaging, cerebrospinal fluid laboratory findings, and evoked electrical potential.[3] In 2001, the McDonald tool was developed to assist in interpreting these various test results, in an effort to diagnose patients sooner and with greater sensitivity.[6] As health technologies have advanced, so too has the tool as outlined by the many revisions to the original writing:[6] in 2005,[7] 2010,[8] and 2017.[9]

Both CIS and relapsing-remitting multiple sclerosis (RRMS) are managed with a variety of pharmacotherapies, such as: corticosteroids, immunosuppressants, immunomodulators, and drugs targeted to particular symptoms.[2-4]

The goals of therapy in CIS are to delay the onset of additional relapses and progression to MS.[10] Whereas, the goals of therapy in RRMS include the management of flare-ups,

prevention of future exacerbations, management of ongoing signs and symptoms (e.g., muscle spasms, pain), and supportive care.[3]

Recently, the immunomodulating properties of minocycline, a tetracycline antibiotic, were discovered to impact neurological diseases in animal experiments.[11] Further studies revealed the drug's anti-inflammatory and neuroprotective effects,[12] making it a interesting prospect for MS treatment.

The objective of the current report is to evaluate the clinical effectiveness and evidence-based guidelines regarding the use of minocycline in CIS and RRMS.

Research Questions

1. What is the clinical effectiveness of minocycline for relapsing-remitting multiple sclerosis?

2. What is the clinical effectiveness of minocycline for clinically isolated syndrome?

3. What are the evidence-based guidelines regarding minocycline for relapsing-remitting multiple sclerosis or clinically isolated syndrome?

Key Findings

One relevant randomized controlled trial was identified regarding the clinical effectiveness of minocycline for clinically isolated syndrome. No evidence regarding the clinical effectiveness of minocycline for relapsing-remitting multiple sclerosis was identified. Furthermore, no evidence-based guidelines were identified regarding minocycline for relapsing-remitting multiple sclerosis or clinically isolated syndrome.

Limited evidence from this single study indicated that the risk of conversion from clinically isolated syndrome to multiple sclerosis at six months was statistically significantly lower in patients treated with minocycline versus placebo. However, the differences in outcomes were not sustained at 24 months. Relapse rates at six and 24 months were not statistically different between groups. The mean change in Expanded Disability Status Scale score between baseline and the end of the study was not statistically different between groups. Furthermore, the between-group differences at six months on magnetic resonance imaging outcomes (lesions volume, new enhancing lesions, cumulative number of lesions) in favour of minocycline were no longer significant at 24 months, when results were adjusted for the number of enhancing lesions at baseline. Patients treated with minocycline were also found to have statistically significantly greater numbers of adverse events compared to patients treated with placebo. Results from this single study should be interpreted with caution.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts

were minocycline and multiple sclerosis or clinically isolated syndrome. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 16, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1,3: Adult patients with Relapsing-Remitting Multiple Sclerosis Q2,3: Adult patients with Clinically Isolated Syndrome
Intervention	Q1-3: Minocycline
Comparator	Q1: Multiple Sclerosis therapies (i.e., interferon beta-1a, interferon beta-1b, glatiramer acetate, dimethyl fumarate, ocrelizumab, teriflunomide, peginterferon beta), placebo Q2: Clinically Isolated Syndrome therapies (i.e., interferon beta-1a, interferon beta-1b, glatiramer acetate) placebo Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., time to conversion to Multiple Sclerosis [McDonald, Clinically definite Multiple Sclerosis]), Q2: Clinical effectiveness (e.g., disability, relapse, changes in number and volume of lesions (identified on Magnetic Resonance Imaging), health related quality of life), harms (e.g., adverse events) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were in a language other than English, or were published prior to 2009. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trial (RCT) was critically appraised by one reviewer using the Scottish Intercollegiate Guideline Network Methodology Checklist 2: Randomised Controlled Trials.[13] Summary scores were not calculated for the included study; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 105 citations were identified in the literature search. Following screening of titles and abstracts, 90 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. Although the grey literature was searched, no potentially relevant publications were retrieved. Of the potentially relevant

articles, 14 publications were excluded for various reasons, and one publication, an RCT,[14] met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Appendix 5 includes five additional references that did not meet the inclusion criteria of this report but may be of interest.

Summary of Study Characteristics

One relevant RCT[14] was identified and included in this review. No relevant health technology assessments, systematic reviews, meta-analyses, non-randomized studies, or evidence-based guidelines were identified. Detailed characteristics are available in Appendix 2, Table 2.

Study Design

One primary study regarding the clinical effectiveness and safety of minocycline in patients who experienced a clinically isolated syndrome (CIS) was identified. This 2017 RCT[14] was a multicentre, randomized, double-blind, placebo-controlled trial.

Country of Origin

The RCT[14] was conducted in Canada.

Patient Population

The RCT[14] focused on 142 adult participants recruited from 12 Canadian MS clinics. Participants had experienced a CIS within the previous 180 days.

Interventions and Comparators

In the RCT,[14] the intervention was 100 mg of minocycline twice daily compared to placebo.

Outcomes

In the RCT, the outcomes of interest were relapse at six and 24 months, conversion to MS at six and 24 months, adverse events (AEs), MS symptoms, and magnetic resonance imaging (MRI) outcomes (i.e., mean lesion volume, cumulative number of new enhancing lesions, and combined number of unique lesions).[14] The 2005 McDonald criteria were to diagnose CIS before the trial began and MS during the trial.[14] This tool relies on objective clinical findings, dissemination of lesions (using MRI findings) in time and space, and paraclinical examination of speed of evolution.[7] A summary of diagnostic requirements for MS in patients with a disease that progresses from onset include: 1) one year of disease progression, as well as 2) two of the following: i) a positive brain MRI, ii) a positive spinal cord MRI, or iii) positive cerebrospinal fluid findings.[7] In addition, authors used the Expanded Disability Status Scale (EDSS)[16] to assess neurologic impairment at baseline and end of study. The scale progresses from 0 (normal) to 10.0 (death due to MS), indicating an increasing degrees of disability,[16]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publication are provided in Appendix 3, Table 3.

The RCT[14] had several strengths, such as: a clear description of objectives, interventions, main outcomes, population characteristics and eligibility criteria. Rigorous randomization

appears to have been followed along with allocation concealment. Participants and investigators appear to have been adequately blinded. The trial's protocol was registered prior to the start of the study. Estimates of random variability were reported, and the data analyses were planned at the outset. Partway through the trial, the 2010 revision to the McDonald criteria was issued, which would have changed the baseline classification of some participants (i.e., from having a diagnosis of CIS to a diagnosis of MS). Despite this, the authors did not change the instrument and maintained the use of the 2005 definition throughout the study.[14] Note that the McDonald criteria were further revised in 2017,[9] including some changes specific to patients with CIS. For instance, the presence of cerebrospinal fluid oligoclonal bands were added as a predictor of a second exacerbation,[9] which accelerates the diagnosis of MS in CIS patients. As such, it is conceivable that worse-off CIS patients were included in the study that would be considered to have MS with the 2017 version of the tool. In addition, the refining of the diagnostic criteria tool introduces uncertainty with respect to the applicability of the RCT's results to contemporary patients. Further limitations of the study included: an imbalance of certain baseline characteristics, such as a greater number of patients with multifocal symptoms and patients with two or more lesions in the placebo group. This may have biased the results in favour of the intervention group. Furthermore, discontinuation and withdrawal rates were dissimilar between groups. For instance, nine minocycline participants withdrew before six months (three due to active disease, three due to loss to follow-up, two due to AEs, and one due to not being able to meet the time commitment) and an additional five discontinued the study because of AEs but continued follow-up. Over the same time period, the placebo group had four withdrawals (two due to the time commitment, one due to loss to follow-up, and one deviation from protocol) and four discontinuations (two due to AEs, one due to active disease, and one due to planning for pregnancy). Lastly, although the trial was multi-centric, results were not stratified by site and an analysis of potential site differences was not done.

Summary of Findings

A detailed summary of findings is provided in Appendix 4, Table 4.

Clinical Effectiveness of Minocycline for Relapsing-Remitting Multiple Sclerosis

No relevant evidence regarding the clinical effectiveness of minocycline for RRMS was identified; therefore, no summary can be provided.

Clinical Effectiveness of Minocycline for Clinically Isolated Syndrome

Relapse rate

Authors of the RCT[14] reported non-significantly higher relapse rates within six months (unadjusted numbers) for the placebo group(P = 0.085). The between-group difference remained non-significant at 24 months (P = 0.25).

Conversion to MS

Authors of the RCT[14] reported that 33.4 % of patients in the minocycline group compared with 61.0% in the placebo group, had converted to MS within six month of randomization (unadjusted risk), a statistically significant difference of 27.6% (95% CI, 11.4% to 43.9%; P = 0.001).[14] This unadjusted value met the author's prespecified clinically meaningful difference of 25%.[14] However, when looking at results adjusted according to number of enhancing lesions at baseline, 43.0% of patients in the minocycline group compared with 61.5% in the placebo group, had converted to MS within six month of randomization , a statistically significant difference of 18.5% (95% CI, 3.7% to 33.3%; P = 0.01).[14] Although

statistically significant, this latter value may not be clinically significant since the overall sample size was calculated based on a 25% difference in risk.[14] The unadjusted between-group difference was no longer significant at 24 months (16.7%, 95% CI, –0.6% to 34.0%; *P* = 0.06), at which time 55.3% of patients in the minocycline group compared with 72.0% of those in the placebo group, had converted to MS.[14] Similarly, the 24-month between-group difference was no longer significant when looking at the results adjusted according to number of enhancing lesions at baseline (11.2%; 95% CI, –4.8% to 27.1%; *P* = 0.17), at which time 63.0% of patients in the minocycline group compared with 74.2% of those in the placebo group, had converted to MS.[14]

MRI outcomes

The authors of the RCT[14] reported on the six-month changes from baseline in mean lesion volume, mean cumulative number of new enhancing lesions, and mean cumulative combined number of unique lesions.[14]

For changes in lesion volume at six months, adjusted according to number of enhancing lesions at baseline, authors reported lesion volume deceased in the minocycline group and increased in the placebo group, with a significant between-group difference (*P* = 0.049).[14] At 24 months, the adjusted differences were no longer significant. However, the unadjusted mean value of the between-group difference remained significant (*P* = 0.02) at six and 24 months.

For changes in cumulative number of new lesions at six months, adjusted according to number of enhancing lesions at baseline, authors reported significantly fewer in the minocycline group(*P* = 0.02).[14] At 24 months, the adjusted differences were no longer significant. However, the unadjusted mean value of the between-group difference remained significant at six (*P* < 0.001) and 24 months (*P* = 0.001).

For changes in cumulative combined number of unique lesions at six months, adjusted according to number of enhancing lesions at baseline, authors reported significantly fewer in the minocycline group(*P* = 0.007).[14] At 24 months, the adjusted differences were no longer significant. However, the unadjusted mean value of the between-group difference remained significant (*P* < 0.001) at six and 24 months.

EDSS

At the end of the study, authors of the RCT[14] reported an overall mean change in EDSS of –0.26 (SE = 0.13) points in the minocycline group compared to –0.17 (SE = 0.12) points in the placebo group (unadjusted numbers), a non-statistically significant difference of 0.09 (95% CI, –0.26 to 0.44; *P* = 0.60). Negative values indicate improvement in EDSS scores.

AEs

Authors of the RCT[14] reported significantly greater numbers of participants with adverse events in the minocycline group (86.1%) compared to the placebo group (61.4%; *P* = 0.001).[14] Patients in the minocycline group had a statistically significant greater number of the following AEs in comparison with the placebo group: rash (15.3% versus 2.9%), dental discoloration (8.3% versus 0%, respectively), and dizziness (13.9% versus 1.4%, respectively).[14] The incidence of transient grade 3 or 4 AEs detected on laboratory tests was not significantly different between groups (2.8% of the minocycline group and 2.9% of placebo group; *P* = 0.98).[14] Five serious AEs, requiring hospitalisation, were experienced by four patients: one in the minocycline group and three in the placebo group (*P* = 0.30).[14]

Evidence-Based Guidelines Regarding Minocycline for Relapsing-Remitting Multiple Sclerosis or Clinically Isolated Syndrome

No relevant evidence-based guidelines were identified regarding minocycline for RRMS or CIS; therefore, no summary can be provided.

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 3; however, additional limitations exist. The main limitations of this review are related to the limited number of research studies identified, resultant limited analytical sample, and the outdated tool used for diagnosis of patients at baseline and for the measurement of the primary outcome in the analytical sample. This may have resulted in worse-off patients being included in the study that would now considered to have MS using the 2017 version of the tool. Furthermore, there was no evidence on the clinical effectiveness of minocycline for RRMS, as well as no evidence-based guidelines regarding minocycline for CIS and RRMS. This suggests that additional research in this area is required.

Conclusions and Implications for Decision or Policy Making

This report identified one relevant RCT regarding the clinical effectiveness of minocycline for CIS.[14]

This study showed that the risk of conversion to MS (from CIS) at six months was significantly lower in patients treated with minocycline compared to those treated with placebo.[14] However, the between-group difference in conversion rate favouring minocycline was no longer significant after 24 months of treatment.[14] Relapse rates at six and 24 months, and the mean change in EDSS score between baseline and the end of the study, were not statistically different between groups.[14] Furthermore, between-group differences at six months on magnetic resonance imaging outcomes (lesions volume, new enhancing lesions, cumulative number of lesions) in favour of minocycline were no longer significant at 24 months, when results were adjusted for the number of enhancing lesions at baseline. Patients treated with minocycline were also found to have statistically significantly greater numbers of adverse events compared to patients treated with placebo. Additionally, the authors used a diagnosis instrument which has since received two major revisions, introducing uncertainty with respect to the applicability of their results in the context of the current diagnostic paradigm.

The limitations of the included study should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the clinical effectiveness of minocycline for RRMS or CIS, especially by way or large, methodologically-sound RCTs or well-designed meta-analyses would help reduce this uncertainty.

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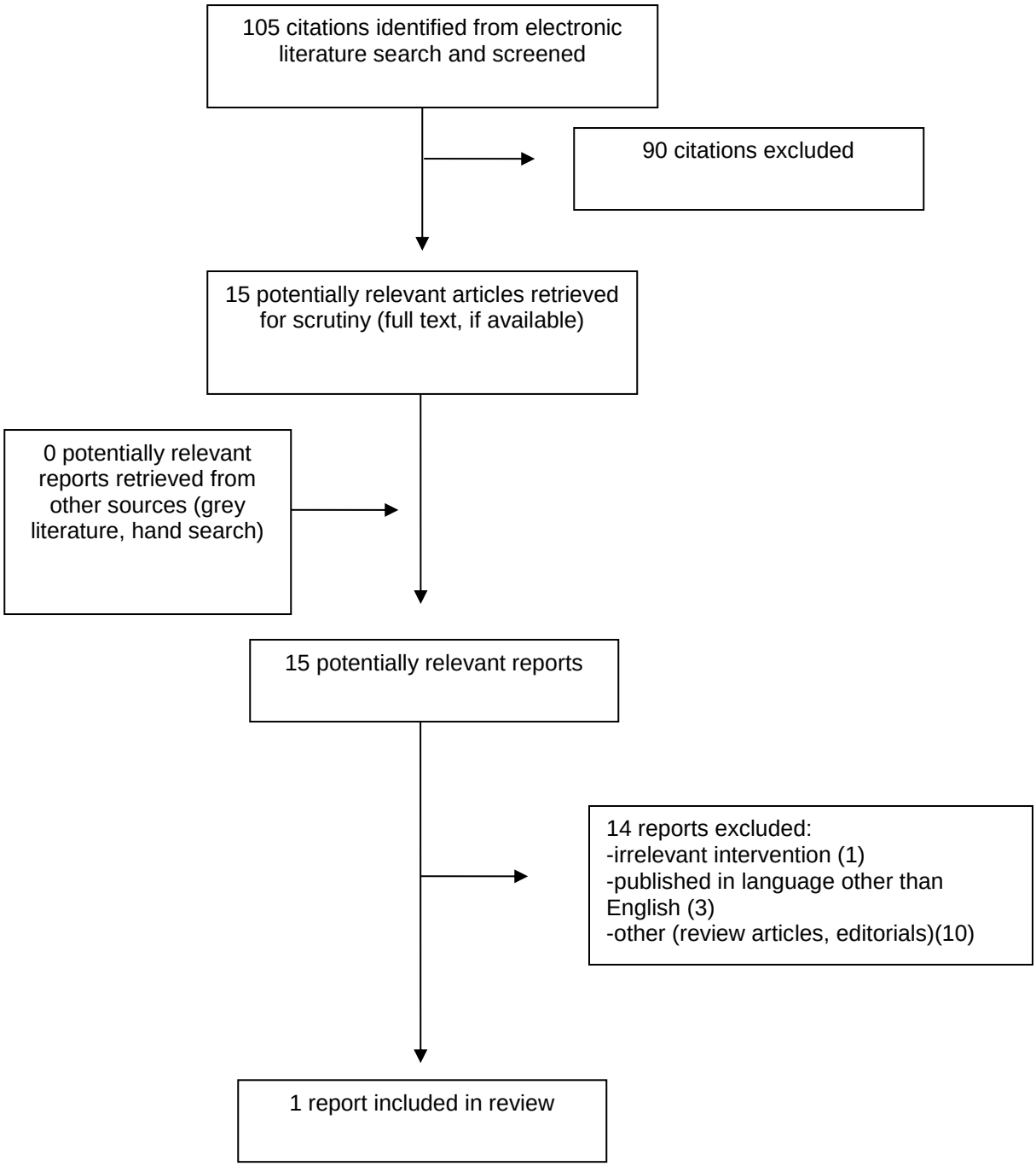
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Metz, 2017[14] **Canada**	**Study design**: multicenter, randomized, double-blind, placebo-controlled trial. **Setting**: twelve Canadian MS clinics. **Objective**: to determine whether minocycline reduces the risk of conversion from a first clinical demyelinating event to multiple sclerosis diagnosed on the basis of the 2005 McDonald criteria.	Adults (18 to 60 years) who experienced a CIS within the previous 180 days and with at least two lesions, visible on MRI, larger than three millimetres in diameter. **Number of patients in analytical sample**: 142 participants: 72 in the intervention group. **Mean age of analytical sample**: 35.9 years in intervention group; 35.7 years in placebo group. **Sex of analytical sample**: 75.0% female in intervention group; 61.4% in placebo group.	**Intervention**: 100 mg minocycline twice daily **Comparator**: placebo	**Outcomes**: - Conversion to MS - Relapse - EDSS - AEs - MS symptoms - Treatment adherence - Cranial MRI **Follow-up**: Up to 24 months or until a diagnosis of MS was confirmed.

AE = adverse event; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using the Scottish Intercollegiate Guideline Network Methodology Checklist 2: Randomised Controlled Trials[13]

Strengths	Limitations
Metz, 2017[14]	
- The study addressed an appropriate and clearly focused question. - The assignment of subjects to treatment groups was randomised (one to one ratio in permuted blocks of four, generated by the trial biostatistician, with stratification according to site and risk for conversion to MS). - Allocation concealment was described, (e.g., only the central pharmacist knew which sequentially numbered bottle medication contained minocycline or placebo; the placebo visually matched the intervention drug). - Subjects and investigators were blinded to the intervention. - It appears that the only interventional difference between the groups was the treatment under investigation. - The outcomes were measured in a standard, valid and reliable way (e.g., MRI, McDonald criteria) - All participants were analysed in the group to which they were randomly allocated (intention to treat analysis). - The trial had an a priori protocol and was registered (NCT00666887) - Funding source was declared (the MS Society of Canada), and they had no role in data analysis, interpretation, review of the manuscript, or decision to publish. - Authors disclosed potential conflicts of interests, including receiving funding from drug manufacturers.	- Although the treatment and control groups were generally similar at the start of the trial; they had baseline imbalances (e.g., a greater number of patients had multifocal symptoms or two or more lesions in the placebo group than in the minocycline group). Despite these imbalances, both unadjusted and adjusted findings were in the same direction, which increases our confidence in the results. - Discontinuation and withdrawal rates were dissimilar between groups. For instance, nine minocycline participants withdrew before six months (three due to active disease, three due to loss to follow-up, two due to AEs, and one due to not being able to meet the time commitment) and an additional five discontinued the study because of AEs but continued follow-up. Over the same time period, the placebo group had four withdrawals (two due to the time commitment, one due to loss to follow-up, and one deviation from protocol) and four discontinuations (two due to AEs, one due to active disease, and one due to planning for pregnancy). - Although a power calculation was performed and the authors determined they needed 154 participants to detect an 80% absolute difference of 25% in risk of conversion from CIS to MS, this number of participants was not attained (142 participants total). - Although the trial was multi-centric, results were not stratified by site and an analysis of potential site differences was not done.

MRI = magnetic resonance imaging; MS = multiple sclerosis.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Metz, 2017[14]	
Relapse within six months *Unadjusted risk*: • Minocycline: 7 of 72 participants (9.7%), • Placebo: 14 of 70 participants (20.0%), • Between group unadjusted difference of 10.3 (95% CI, –1.3 to 21.9) (*P* = 0.085) **Relapse within 24 months** *Unadjusted risk*: • Minocycline: 11 of 72 participants (15.3%), • Placebo: 16 of 70 participants (22.9%), • Between group unadjusted difference of 7.6 (95% CI, –5.3 to 20.5) (*P* = 0.25) **Conversion to MS within six months** *Unadjusted risk:* • Minocycline: 23 of 72 participants (33.4%), • Placebo: 41 of 70 participants (61.0%), • Between group unadjusted risk difference of 27.6% (95% CI, 11.4% to 43.9%) (*P* = 0.001) *Risk Adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 43.0%, • Placebo: 61.5%, • Between group adjusted risk difference of 18.5% (95% CI, 3.7% to 33.3%) (*P* = 0.01) **Conversion to MS within 24 months** *Unadjusted risk:* • Minocycline: 34 of 72 participants (55.3%), • Placebo: 47 of 70 participants (72.0%), • Between group unadjusted risk difference of 16.7% (95% CI, –0.6% to 34.0%) (*P* = 0.06) *Risk Adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 63.0%, • Placebo: 74.2%, • Between group adjusted risk difference of 11.2% (95% CI, –4.8% to 27.1%) (*P* = 0.17) **MRI outcomes at six months** Measured in 67 of 72 minocycline participants and 65 of 70 placebo participants: • Change in mean lesion volume on T_2-weighted MRI: *Unadjusted mean values:* • Minocycline: –343 mm^3 (SE = 202 mm^3), • Placebo: 317 mm^3 (SE = 206 mm^3),	"In conclusion, this trial showed that the risk of conversion from a clinically isolated syndrome to multiple sclerosis at 6 months was significantly lower with minocycline than with placebo in both the unadjusted and adjusted analyses. This trial met a prespecified outcome of an absolute difference of 25 percentage points in the risk of conversion to multiple sclerosis in the unadjusted analysis, and although the risk difference was smaller after adjustment for baseline imbalances, the differences remained significant and all MRI outcomes at 6 months favored minocycline over placebo. The between-group differences in outcomes were not sustained at 24 months."[14] (*p*2131)

Main Study Findings	Authors' Conclusion
• Between group unadjusted mean difference of 661 mm^3 (95% CI, 96 mm^3 to 1,226 mm^3) (*P* = 0.02) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: –290 mm^3 (SE = 231 mm^3), • Placebo: 295 mm^3 (SE = 222 mm^3), • Between group adjusted mean difference of 584 mm^3 (95% CI, 3 mm^3 to 1,166 mm^3) (*P* = 0.049) • Mean cumulative number of new enhancing lesions on MRI: *Unadjusted mean values:* • Minocycline: 0.18 (SE = 0.06), • Placebo: 0.95 (SE = 0.24), • Between group unadjusted mean difference of 0.77 (95% CI, 0.29 to 1.26) (*P* < 0.001) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 0.23 (SE = 0.08), • Placebo: 0.58 (SE = 0.14), • Between group adjusted mean difference of 0.35 (95% CI, 0.05 to 0.65) (*P* = 0.02) • Mean cumulative combined number of unique lesions: *Unadjusted mean values:* • Minocycline: 0.60 (SE = 0.16), • Placebo: 3.00 (SE = 0.67), • Between group unadjusted mean difference of 2.40 (95% CI, 1.06 to 3.75) (*P* < 0.001) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 0.83 (SE = 0.19), • Placebo: 1.84 (SE = 0.34), • Between group adjusted mean difference of 1.01 (95% CI, 0.25 to 1.77) (*P* = 0.007) **MRI outcomes at 24 months** • Change in mean lesion volume on T_2-weighted MRI: *Unadjusted mean values:* • Minocycline: –346 mm^3 (SE = 204 mm^3), • Placebo: 314 mm^3 (SE = 207 mm^3), • Between group unadjusted mean difference of 660 mm^3 (95% CI, 91 mm^3 to 1,229 mm^3) (*P* = 0.02) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: –295 mm^3 (SE = 232 mm^3), • Placebo: 288 mm^3 (SE = 224 mm^3), • Between group adjusted mean difference of 583 mm^3 (95% CI, –2 mm^3 to 1,168 mm^3) (*P* = 0.051)	

Main Study Findings	Authors' Conclusion
• Mean cumulative number of new enhancing lesions on MRI: *Unadjusted mean values:* • Minocycline: 0.28 (SE = 0.09), • Placebo: 0.98 (SE = 0.24), • Between group unadjusted mean difference of 0.70 (95% CI, 0.21 to 1.19) (*P* = 0.001) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 0.41 (SE = 0.12), • Placebo: 0.69 (SE = 0.16), • Between group adjusted mean difference of 0.27 (95% CI, –0.12 to 0.66) (*P* = 0.17) • Mean cumulative combined number of unique lesions: *Unadjusted mean values:* • Minocycline: 1.01 (SE = 0.22), • Placebo: 3.11 (SE = 0.62), • Between group unadjusted mean difference of 2.09 (95% CI, 0.80 to 3.39) (*P* < 0.001) *Mean values adjusted according to number of lesions enhanced on MRI at baseline:* • Minocycline: 1.58 (SE = 0.33), • Placebo: 2.01 (SE = 0.36), • Between group adjusted mean difference of 0.43 (95% CI, –0.53 to 1.39) (*P* = 0.38) **EDSS** *At baseline, median (range):* • Minocycline: 1.5 (0 to 3.0) • Placebo: 1.5 (0 to 4.5) *Overall mean change at end of study, unadjusted:* • Minocycline: –0.26 (SE = 0.13) • Placebo: –0.17 (SE = 0.12) • Between group unadjusted mean difference of 0.09 (95% CI, –0.26 to 0.44) (*P* = 0.60) **Adverse events** Overall reports of any AEs: • Minocycline: 86.1% • Placebo: 61.4%, *P* = 0.001 Rash: • Minocycline: 15.3% • Placebo: 2.9%, *P* = 0.01 Dental discoloration: • Minocycline: 8.3% • Placebo: 0%, *P* = 0.01 Dizziness: • Minocycline: 13.9% • Placebo: 1.4%, *P* = 0.005	

Main Study Findings	Authors' Conclusion
Transient grade 3 or 4 AE detected on laboratory test: • Minocycline: 2.8% • Placebo: 2.9%; *P* = 0.98 Serious AEs, hospitalisation. Five AEs were experienced by: • Minocycline: one participant • Placebo: three participants; *P* = 0.30	

AE = adverse event; CI = confidence interval; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; SE = standard error.

Appendix 5: Additional References of Potential Interest

Clinical Practice Guidelines

Methodology Unclear

Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci.* 2013 May;40(3):307-323. PubMed: PM23603165

Randomized Controlled Trials

Alternative Intervention – Minocycline as Add-On Therapy

Sorensen PS, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study. *Eur J Neurol.* 2016 May;23(5):861-870.
PubMed: PM26848561

Conference Abstracts and Posters

Metz LM, Li D, Traboulsee A, et al. Minocycline reduces the relative risk of multiple sclerosis in people experiencing their first clinical demyelinating event by 44.6%: Results of a phase III double-blind placebo controlled Canadian multicentre clinical trial. *Mult Scler*. 2015 September;1):780-781.

Metz L, Traboulsee A, Li D, et al. Randomized trial of minocycline for clinically isolated syndrome and early single relapse multiple sclerosis: study design, participant characteristics, and recruitment challenges. *Neurology.* 2014 April;82(10 SUPPL. 1).

Sorensen PS, Sellebjerg F, Lycke J, et al. No beneficial effect of minocycline as add-on therapy to interferon-b-1a for the treatment of relapsing-remitting multiple sclerosis: results of a large double-blind, randomised, placebo-controlled trial. *Mult Scler*. 2012 October;1):431-432.