Annex 1. GRADE evidence summary tables

5-1. GRADE Table - 6 months of (H)REZ compared with more than 6 months of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months of (H)REZ compared to more than 6 months of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months of (H)REZ	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse 6 months of (H)REZ versus more than 6 months of (H)REZ												
15	observational studies	serious	not serious[a]	not serious	serious[b]	All plausible residual confounding would reduce the demonstrated effect	254/262 (96.9%)[c]	999/1088 (91.8%)[d]	**adjusted OR 2.4** (1.0 to 5.5)[e]	**40 more per 1,000** (from 0 fewer to 80 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL
Subgroup analysis : treatment success versus treatment failure/relapse of 6 months of REZ compared with more than 6 months of REZ												
13	observational studies	serious	not serious[a]	not serious	serious[b]	All plausible residual confounding would reduce the demonstrated effect	136/142 (95.8%)	701/785 (89.3%)	**adjusted OR 2.5** (0.9 to 7.5)[g]	**50 more per 1,000** (from 10 fewer to 100 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin, for 6 months of (H)REZ versus more than 6 months of (H)REZ[h]												
10	observational studies	serious	serious[i]	not serious	serious	none	1/168 (0.6%)[j]	43/992 (4.3%)[k]	**adjusted OR 0.2** (0.0 to 1.7)[l]	**10 more per 1,000** (from 60 fewer to 40 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. Inconsistency based on I squared.
b. Broad confidence interval.
c. Of the 262 treated, 120 had isoniazid for one month or more and 142 did not. Stratification by resistance to SM did not show any significant difference in treatment success between the intervention and comparator groups.
d. Of the 1088 treated, 303 had isoniazid for one month or more and 785 did not. Stratification by resistance to SM did not show any significant difference in treatment success between the intervention and comparator groups.
e. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 262 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
f. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
g. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 140 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred, but not analysed).
i. Completeness of testing for the acquisition of resistance to rifampicin and the procedures followed for testing may have differed between individuals within the same cohort and between patient series.
j. Of the 168 treated, 84 had isoniazid for one month or more and 84 did not.
k. Of the 992 treated, 263 had isoniazid for one month or more and 729 did not.
l. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 168 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.

5-2. GRADE Table - 6 months or more of (H)REZ plus fluoroquinolone compared with 6 months or more of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017) [a]
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months or more of (H)REZ plus fluoroquinolone	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ												
15	observational studies	serious	not serious[b]	not serious	serious[c]	Strong association all plausible residual confounding would reduce the demonstrated effect[d]	245/251 (97.6%)[e]	1253/1350 (92.8%)[f]	**adjusted OR 2.8** (1.1 to 7.3)[g]	**50 more per 1,000** (from 0 more to 90 more)[h]	⨁⨁◯◯ LOW	CRITICAL
Death versus success/treatment failure/relapse in (H)REZ-FQ vs (H)REZ[i]												
15	observational studies	serious	not serious[b]	not serious	not serious	All plausible residual confounding would reduce the demonstrated effect[d]	25/524 (4.8%)[j]	97/2174 (4.5%)[k]	**adjusted OR 0.7** (0.4 to 1.1)[l]	**20 fewer per 1,000** (from 50 fewer to 0 fewer)[h]	⨁⨁◯◯ LOW	CRITICAL
Death versus success/treatment failure/relapse in REZ-FQ vs REZ (subgroup analysis in patients with no isoniazid use)[i]												
14	observational studies	serious	not serious[b]	not serious	very serious[m]	All plausible residual confounding would reduce the demonstrated effect[d]	8/219 (3.7%)	41/1054 (3.9%)	**adjusted OR 0.4** (0.2 to 1.1)[n]	**20 fewer per 1,000** (from 60 fewer to 20 more)[h]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ[o]												
10	observational studies	serious	serious[p]	not serious	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect	1/221 (0.5%)	44/1160 (3.8%)	**adjusted OR 0.1** (0.0 to 1.2)[q]	**30 fewer per 1,000** (from 60 fewer to 0 fewer)[h]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse for 6 months or more of REZ plus fluoroquinolone compared to 6 months or more of REZ: subgroup analysis in patients without isoniazid												
14	observational studies	serious	not serious[b]	not serious	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect [d]	131/135 (97.0%)	837/927 (90.3%)	**adjusted OR 5.4** (1.8 to 16.6)[r]	**130 more per 1,000** (from 40 fewer to 230 more)[h]	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse for 6 months or more of (H)REZ plus fluoroquinolone compared to 6 months or more of (H)REZ: subgroup analysis in patients using moxifloxacin/levofloxacin/gatifloxacin as fluoroquinolones												
15	observational studies	serious	not serious[b]	not serious	very serious[m]	all plausible residual confounding would reduce the demonstrated effect[d]	161/165 (97.6%)[s]	1253/1350 (92.8%)[f]	**adjusted OR 2.9** (0.9 to 9.3)[t]	**60 more per 1,000** (from 20 fewer to 140 more) [h]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. The median duration of use of fluoroquinolones in ≥6months (H)REZ+FQ regimens was of 6.1 months (interquartile range 3.5; 8.4); for rifampicin 9.0 (7.2; 11.1); for ethambutol 9.0 (7.3; 11.1) and for pyrazinamide 8.9 (6.8; 10.7). In one large database, with 137 patients with this regimen, start dates of each drug were available and therefore it was possible to calculate the delay between start of rifampicin and fluoroquinolones: median 1.4 months (IQR 0.9; 2.3)
b. Based on I squared
c. The confidence interval is broad.
d. Addition of FQ may represent confounding by indication.
e. Of the 251 treated, 116 had isoniazid for one month or more and 135 did not.
f. Of the 1350 treated, 423 had isoniazid for one month or more and 927 did not.
g. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 248 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
i. Mortality analysis cannot take into account duration of specific regimens because death truncates duration (outcome determined the independent variable of duration). Mortality analysis thus includes all cases who received (H)REZ+FQ or (H)REZ regardless of duration. Observations contributing to mortality analysis are therefore different from those included in analysis of treatment success.
j. Of the 524 in intervention, 305 had isoniazid for one month or more and 219 did not.
k. Of the 2174 in control, 1120 had isoniazid for one month or more and 1054 did not.
l. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 522 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
m. The confidence interval is broad and includes one.
n. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 205 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
o. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred, but not analysed).
p. Completeness of testing for the acquisition of resistance to rifampicin and the procedures followed for testing may have differed between individuals within the same cohort and between patient series.
q. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 220 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
r. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 127 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
s. Of the 165 treated, 67 had isoniazid for one month or more and 98 did not.
t. Propensity scores odd ratio (aOR) based on matched pairs for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 164 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.

5-3. GRADE Table - 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ

Author(s): Dick Menzies, Federica Fregonese (McGill University, Montréal, Canada)
Date:
Question: 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ for adults and children with isoniazid-resistant tuberculosis in whom resistance to rifampicin has been excluded (IPD ANALYSIS 2017)
Setting: Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis
Bibliography: Fregonese F, Menzies D. Individual-Patient Data (IPD) meta-analysis of isoniazid-resistant tuberculosis (UNDER REVIEW FOR PUBLICATION).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S	6 months or more of (H)REZ	Relative (95% CI)	Absolute (95% CI)		
Treatment success versus treatment failure/relapse for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ												
23	observational studies	serious	not serious[a]	not serious	not serious	none	271/325 (83.4%)[b]	1253/1350 (92.8%)[c]	**adjusted OR 0.4** (0.2 to 0.7)[d]	**120 fewer per 1,000** (from 190 fewer to 60 fewer)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse: subgroup analysis in patients without isoniazid												
14	observational studies	serious	not serious[a]	not serious	very serious[f]	none	89/107 (83.2%)	837/927 (90.3%)	**adjusted OR 0.5** (0.2 to 1.2)[g]	**80 fewer per 1,000** (from 170 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Death versus success/treatment failure/relapse in (H)REZ-S vs (H)REZ[h]												
23	observational studies	serious	not serious[a]	not serious	very serious[f]	none	40/763 (5.2%)[i]	103/2263 (4.6%)[i]	**adjusted OR 0.9** (0.6 to 1.3)[k]	**10 fewer per 1,000** (from 30 fewer to 20 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Death versus success/treatment failure/relapse: subgroup analysis in patients without isoniazid[l]												
14	observational studies	serious	not serious[a]	not serious	very serious[f]	none	6/136 (4.4%)	41/1054 (3.9%)	**adjusted OR 1.2** (0.4 to 4.1)[m]	**0 fewer per 1,000** (from 50 fewer to 60 more)[e]	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of resistance to rifampicin, for 6 months or more of (H)RE and up to 3 months of Z, plus up to 3 months of S compared to 6 months or more of (H)REZ[n]												
14	observational studies	serious	serious	not serious	very serious[o]	none	6/58 (10.3%)	44/1160 (3.8%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence Interval

Explanations

a. Based on I squared.
b. Of the 325 treated, 218 had isoniazid for one month or more and 107 did not.
c. Of the 1350 treated, 423 had isoniazid for one month or more and 927 did not.
d. Propensity scores odd ratio (OR) adjusted for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Poly-resistance was 47% in the group taking 6 or more(H)RE 3Z 3SM as compared with <1% in the group taking 6 or more (H) REZ.) Adjusted OR was calculated on 296 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope.
e. The risk difference (absolute effect) is estimated based on a fixed effects generalized linear mixed model, using propensity score matching method. The adjusted OR should be considered the more robust and correct estimate as it is based on a random effects PS matched model (random intercept and random slope).
f. Confidence interval is broad.
g. Propensity scores odd ratio (OR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used. Adjusted OR was calculated on 105 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
h. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with (H)REZ+SM vs (H)REZ regardless of duration. Hence the observations contributing to mortality (n=3026) analysis are different from observations included in analysis of treatment success (n=1675), even if analysis was done in the same datasets (n=23)- for mortality we consider all duration of regimens (and not only 6 or more (H)RE, up to 3m of Z and up to 3 months of SM, as we do for the success analysis), therefore we have more patients.
i. Of the 763 treated, 627 used isoniazid for one month or more and 136 did not.
j. Of the 2263 treated, 1209 used isoniazid for one month or more and 1054 did not.
k. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 756 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
l. Mortality analysis cannot take into account duration of specific regimens because of death truncated duration (outcome determined the independent variable of duration). Therefore the mortality analysis included all cases who received regimens with REZ+SM vs REZ regardless of duration. Hence the observations contributing to this mortality analysis are different from observations included in analysis of treatment success for 6 months RE, up to 3 months of Z and up to 3 months of SM versus 6 months or more of REZ.
m. Propensity scores odd ratio (aOR) based on pairs matched for: sex, age, HIV, past TB treatment, AFB, poly-resistance (to EMB,PZA,SM if used); calculated on 133 pairs, matching by CALIPER=0.02 with replacement, accounting for matched nature of data in the calculation of standard errors. Results of models run with random intercept and slope for pairs.
n. Analysis restricted to datasets providing information on the acquisition of resistance to rifampicin during treatment (amplification of resistance to other antituberculous agents occurred but not analysed).
o. Not possible to calculate adjusted OR and 95% confidence interval as difficult matching for differences between groups. Annex 5. Evidence-to-Decision Tables.