Network meta-analysis of infliximab biosimilars for the treatment of rheumatoid arthritis

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Purpose. This article assesses the relative efficacy and safety of infliximab biosimilars in treatment of patients with rheumatoid arthritis (RA).

Methods. A frequentist, random-effects network meta-analysis was performed to evaluate evidence from randomized controlled trials that examined the use of infliximab biosimilars for treatment of patients with RA. PubMed and MEDLINE and other sources were searched for reports evaluating rates of response to treatment with the reference product (infliximab) vs an infliximab biosimilar. The primary efficacy outcome of interest was the rate of attainment of ACR20 (ie, 20% improvement in American College of Rheumatology core measures). The primary safety outcome was the rate of treatment-related serious adverse events (SAEs). Data were extracted by the primary author, and an assessment for risks of methodological bias was performed for each evaluated study.

Results. Five studies that enrolled a total of 2,499 patients were included. Overall comparisons using odds ratios and 95% confidence intervals (CIs) did not indicate statistically significant differences in response to treatment with biosimilar agents relative to each other or the infliximab reference product. ORs for ACR20 response for biosimilars vs infliximab were as follows: 1.475 (95% CI, 0.940-2.315) for infliximab-axxq, 1.259 (95% CI, 0.854-1.855) for infliximab-dyyb, 0.865 (95% CI, 0.5511.358) for infliximab-qbtx, and 0.832 (95% CI, 0.506-1.367) for infliximab-abda. Similar findings were observed in reported SAE rates among patients treated with the various biosimilars.

Conclusion. ACR20 response appears to be comparable and nonsignificantly different between infliximab biosimilars. In the absence of any meaningful differences in safety or efficacy, biosimilar cost may be the deciding factor in choosing a treatment or agent for formulary inclusion.

Keywords: biosimilar pharmaceuticals, evidence-based medicine, infliximab, meta-analysis, rheumatoid arthritis, tumor necrosis factor inhibitors

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Tumor necrosis factor (TNF) is a proinflammatory endogenous cytokine that plays a role in many inflammatory conditions, including rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, and ulcerative colitis.[1-4] TNF inhibitors may decrease symptoms and slow the progression of disease in these patients.[3,4] Current guidelines from the American College of Rheumatology (ACR) recommend using TNF inhibitors in patients who do not respond to monotherapy with first-line disease-modifying antirheumatic drugs, such as methotrexate.[4]

Numerous TNF inhibitors have been approved by the US Food and Drug Administration (FDA), with the oldest being infliximab (Remicade, Janssen Biotech) which came to market in 1998.[5] In recent years, several biosimilars to infliximab have been developed, including infliximab-dyyb (Inflectra, Pfizer), infliximab-abda (Renflexis, Merck), infliximab-qbtx (Ixifi, Pfizer), and infliximab-axxq (Avsola, Amgen).[6] Biosimilars are highly similar to their respective originator reference products, with only minimal clinical differences in safety, purity, or potency.[7,8] Although noninferiority or equivalency studies of biosimilars and their originator products are conducted, biosimilars are not often directly compared with each other. Thus, there may be unrecognized differences in efficacy or safety between biosimilar agents themselves. This lack of evidence makes it challenging for clinicians, payers, and healthcare organizations to make decisions about drug formularies and clinical care when choosing between biosimilars.

To date, no indirect or head-to-head studies comparing all infliximab biosimilar agents against one another have been published. Therefore, a network meta-analysis may be useful because it allows for multiple comparisons across a range of interventions, even in the absence of direct evidence.[9,10] The objective of the study described here was to evaluate the comparative efficacy and safety of FDA-approved infliximab biosimilars for the treatment of RA using a network meta-analysis framework.

Methods

The study was designed and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension guidelines for network meta-analyses.[10]

Study selection and eligibility criteria. Studies were included if they met the following parameters: a randomized controlled trial (RCT) study design; inclusion of patients diagnosed with RA; evaluation of an FDA-approved infliximab biosimilar in patients who had an incomplete response to methotrexate; and reporting of efficacy in terms of ACR20 response rate (ie, 20% improvement in American College of Rheumatology core measures). There was no minimum sample size requirement for inclusion of a study in the meta-analysis. Studies were excluded if they had a quasi-RCT design, included duplicate data (ie, were repeat publications), or involved patients who were not naïve to infliximab therapy (eg, studies that evaluated switching from Remicade to an infliximab biosimilar). These switching studies were excluded because most were extensions of the original published trials; therefore, it was believed that including them could bias the analysis due to counting of the same patient cohorts multiple times within the network.

Outcome measures. The primary efficacy endpoint was the ACR20 response rate. The ACR20 response rate was chosen because it is often the primary measure of RA treatment efficacy across published studies[11] and is recognized as a core measure of disease activity by ACR.[12] ACR20 is a dichotomous endpoint whose achievement requires 20% or greater improvement in tender and swollen joint counts (per an assessment of prespecified joints), as well as an improvement of ≥20% in 3 of 5 other areas: inflammation (as evidenced by an elevated erythrocyte sedimentation rate or C-reactive protein level), patient assessment of disease activity (based on Likert response scale or specific questions within broader self-assessment instruments), physician assessment of disease activity (based on horizontal visual analog scale or Likert scale assessment), patient assessment of pain (based on horizontal visual analog scale or Likert scale assessment), and patient assessment of

physical function (using any physical function scale, such as the Arthritis Impact Measurement Scale [AIMS] or Health Assessment Questionnaire-Disability Index [HAQ-DI]).[11-13]

The primary safety endpoint was the rate of occurrence of any serious adverse event (SAE). Although SAEs are not always well defined in clinical trials, reporting of SAEs generally follows the definition outlined by FDA, which includes a life-threatening event, death, hospitalization, disability, permanent damage, and other outcomes that may jeopardize the patient or require medical intervention.[14,15] A comparison of rates of specific adverse reactions was not deemed to be feasible due to differences in how they were generally codified and reported in the articles.

Search strategy, information sources, and data extraction. A detailed literature search was conducted using PubMed and MEDLINE databases and Embase to identify relevant articles published up to March 2020. Systematic reviews were also obtained and their reference lists searched for any additional trials that may have been missed. Grey literature was evaluated using the ClinicalTrials.gov website, package labeling, and manufacturer dossiers. The following search terms were used: *infliximab, Remicade, biosimilar, rheumatoid arthritis, CT-P13, Inflectra, SB2, Renflixis, PF-06438179, Ixifi, APB 710,* and *Avsola*. No language restrictions were applied. An example literature search is provided in eTable 1. Search results were downloaded to Microsoft Excel (Microsoft Corporation, Redmond, WA), where duplicate entries were identified and excluded. The primary author independently screened titles and abstracts yielded by the search against the inclusion and exclusion criteria. A second reviewer's expertise was leveraged if an additional, independent evaluation was needed to validate questionable article inclusions. After initial screening, full reports for all titles that appeared to meet the inclusion criteria, as well as those whose appropriateness for inclusion was uncertain, were obtained. The full-text reports were then screened against the inclusion criteria. The following data were extracted using a standardized collection form: study design parameters, sample size, key patient demographics (age, markers of disease severity, etc), information regarding interventions (drug dose, frequency, etc), details related to study efficacy endpoints (primary efficacy outcome, follow-up period, prespecified equivalence

margin, intention-to-treat vs per-protocol methodology, results for primary outcome, etc), and key information related to safety endpoints (primary safety outcome, frequencies and types of of adverse effects [AEs], type of adverse effect, etc). Of note, the abstracted data from the intention-to-treat population in each study were used in the primary efficacy and safety evaluation.

Validity assessment. The Cochrane Risk of Bias Tool (version 2) was used to assess the quality of studies based on the following criteria: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results.[16] Quality of evidence in each domain was then rated as low, high, or unclear. A qualitative synthesis of clinical and methodological heterogeneity was also conducted, as well as an assessment of transitivity.[17,18]

Statistical analysis. Stata version 16.1 (StataCorp LLC, College Station, TX) was used to perform the network meta-analysis using the "mvmeta" and "network" commands, a method that follows a frequentist approach.[17-19] The "network meta inconsistency" command within Stata was used to assess model consistency. A pairwise odds ratio (OR) and 95% confidence interval (CI) was determined to measure the association between a treatment and its efficacy. Results were considered statistically significant if the 95% CI did not contain the value 1. The Confidence in Network Meta-Analysis (CINeMA) Tool (version 1.9.1), which also uses a frequentist approach, was used to generate a corresponding league table comparing the relative effects between agents, including indirect pairwise comparisons between biosimilars.[20] A random-effects model was used for the CINeMA analysis. This same approach was used to perform prespecified sensitivity analyses to evaluate the impact of follow-up period differences on ACR20 response.

The efficacy and safety of each biosimilar agent in the treatment of RA was then arranged in the order of the probability of being ranked as the best-performing agent and displayed via a rankogram. Information on relative effects was converted to a probability that a treatment would be the best, second best, third best, fourth best, or worst by ranking each therapy according to the surface under the cumulative ranking curve (SUCRA). The SUCRA represents a numeric summary of

the overall rank distribution associated with each treatment and supplements graphical representations for a given outcome. The SUCRA value is 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst.[21-23]

Results

Study characteristics. The initial literature search yielded 294 results. After removing duplicates, 192 article titles and abstracts were reviewed, which resulted in 181 exclusions. The most common reason for exclusion was a non-RCT article type. The remaining 11 articles underwent full-text review and, of these, 6 were excluded (Figure 1). Thus, a total of 5 studies that cumulatively enrolled 2,499 patients met inclusion criteria and were included in the analysis. A summary of these studies is provided in Table 1. Figure 2 describes the network diagram, showing the relationship between studies. Given that only 5 studies met the inclusion criteria, the network was limited and reliant on indirect comparative evidence for biosimilar agents. No statistical inconsistency in the model was detected.

Overall, study populations were similar across the articles. Mean patient ages ranged from approximately 50 to 55 years, and mean disease duration ranged from 6.4 to 8.5 years. Included patients across studies also had moderate to severe RA, as determined through assessment of the number of painful joints, number of swollen joints, and a composite measure consisting of the disease activity score for 28 prespecified joints (DAS28) plus scoring components based on C-reactive protein level. Although mostly similar to patient populations in the other evaluated studies, patients in the study of Takeuchi et al[28] may have had slightly less severe disease, as evidenced by a lower mean tender joint count and lower mean DAS28 value. Infliximab and biosimilar dosing and administration parameters were also identical across studies, with a 3-mg/kg dose infused at weeks 0, 2, and 6 and followed by a maintenance dose every 8 weeks thereafter. The primary difference between studies was the duration of follow-up, which ranged from 22 to 54 weeks.

Risk of bias. All 5 of the included studies were determined to have a low overall risk of bias (eFigure 1). Although all studies were randomized, authors of 3 of the 5 studies failed to provide specific details on how the random allocation sequence was generated; however, based on reviewer judgment, this was not deemed to have resulted in a high risk of bias given that these were large, multicenter trials run by experienced clinical trial teams. This decision was acceptable under the Cochrane Risk of Bias Tool (version 2) methodology.[16]

Comparative efficacy. In general, individual study results for efficacy demonstrated equivalence of each biosimilar to the infliximab reference product in terms of ACR20 response (Table 1). Infliximab-axxq[24] and infliximab-dyyb[27,28] were the only products associated with a higher ACR20 response rate than the reference product, whereas infliximab-qbtx[25] and infliximab-abda[26] both were associated with lower response rates (albeit still within the prespecified equivalence margins). Notably, the initial risk difference for infliximab-axxq exceeded the upper bound of the prespecified equivalence margin, such that superiority might be considered; however, this study was not specifically designed to test for superiority, and a post hoc analysis reduced the CI to within the equivalence range.[24]

As described in Table 2, results of the network meta-analysis did not indicate any significant differences in ACR20 response between biosimilar agents relative to each other or the infliximab reference product. Although point estimates exceeded 1 in several comparisons, all 95% CIs crossed 1 and there was wide CI overlap between treatments. Relative to the infliximab reference product, the OR for ACR20 achievement was 1.47 (95% CI, 0.94-2.32) with use of infliximab-axxq;, 1.259 (95% CI, 0.854-1.855) for infliximab-dyyb, 0.865 (95% CI, 0.551-1.358) for infliximab-qbtx, and 0.832 (95% CI, 0.506-1.367) for infliximab-abda. These findings were consistent with results of a predefined sensitivity analysis to evaluate the impact of follow-up period differences on ACR20 response. Specifically, using a shorter follow-up period (30 weeks, as opposed to 54 weeks in the studies of Smolen et al,[26] Yoo et al,[27] and Takeuchi et al[28]) yielded findings nearly identical to those of the primary analysis (see Supplemental eTable 2).

Results of the cumulative ranking probability analysis suggested that infliximab-axxq has a 63.4% chance of being the best-performing agent, while the cumulative probability of it being at least second best is 92% (Table 3 and eFigure 2). The numerical summary of the rank distribution for each treatment (ie, SUCRA ranking probabilities) was 0.9 for infliximab-axxq, 0.7 for infliximab-dyyb, 0.4 for the infliximab reference product, and 0.2 for both infliximab-qbtx and infliximab-abda.

Comparative safety. In general, the rates of AEs differed across individual studies. Overall AE rates were slightly lower in the evaluation of infliximab-axxq by Genovese and colleagues[24] and substantially higher in the evaluation of infliximab-dyyb by Takeuchi and colleagues,[28] in which over 80% of patients in both the biosimilar and reference product arms experienced an AE. The rate of SAEs followed a similar trend, with lower rates reported in the article by Genovese and colleagues[24] and higher rates in the evaluation by Takeuchi and colleagues.[28] Additional details are provided in Table 1. Unfortunately, differences in data reporting made it difficult to compare rates of specific AEs; however, the most commonly reported AEs across the studies were infusion reactions, hypersensitivity, infection, and elevated liver enzymes. Results of our meta-analytic analysis do not suggest any statistically significant differences in SAE rates between biosimilars (Table 4).

Discussion

The study was conducted to compare the relative clinical effectiveness of infliximab and its FDA-approved biosimilars. A network meta-analysis design was chosen to perform an indirect treatment comparison given the lack of head-to-head comparative data on the 5 agents. Overall, the point estimates and 95% CIs of our ACR20 efficacy results suggest that there are no clinically meaningful differences between agents. Although infliximab-axxq was found to have the highest probability of being the best at achieving ACR20 response based on SUCRA ranking probabilities, this result must be interpreted with caution. Specifically, SUCRA rankings may exaggerate small differences in relative effects, especially when based on data from a limited network[23]; this is because SUCRA analysis does not consider the magnitude of the difference in effects. Therefore, it is

possible that the first-ranked treatment may be either slightly better or vastly better than the second-ranked treatment. Additionally, SUCRA values do not account for the possibility of random chance in the model.[23] Similar to the primary efficacy results, the results of analysis of SAEs showed comparable and nonsignificant differences between products. However, these safety results should also be interpreted with caution given that the follow-up period varied between studies from 22 to 54 weeks.[24-28] Likewise, definitions of SAEs were not uniformly defined across studies.

Overall, our findings further support the use of biosimilars in practice and add additional credence to the clinical similarity of the evaluated products. Biosimilars must undergo a rigorous comparison against the reference product in order to gain regulatory approval. Specifically, manufacturers must demonstrate biosimilarity through a totality-of-the-evidence approach, which includes structural and functional analytical studies, pharmacokinetic and pharmacodynamic evaluations, and, if necessary, immunogenicity studies, animal studies, and other comparative clinical trials.[7] However, individual biosimilars are not directly compared with one another. Thus, although a biosimilar may be determined to be equivalent or noninferior to a reference product (depending on the study design), this does not preclude comparative differences between biosimilar agents. Thus, the results of this evaluation may help clinicians, payers, and healthcare organizations make decisions about the choice of biosimilar agent. With all other things being equal, product cost and contractual opportunities may become the primary deciding factor when selecting an infliximab biosimilar for formulary inclusion.

To our knowledge, this is the only published study using a network meta-analytic technique to compare all 4 infliximab biosimilars with one another for the treatment of RA. Previous literature has mostly reported on direct comparisons of biosimilars with the reference product in RCTs. Aside from these head-to-head trials, 2 recent meta-analyses comparing biosimilars to the infliximab reference product have been published. In a study by Bae and colleagues,[29] pooled outcomes data for infliximab-abda and infliximab-dyyb plus methotrexate were compared against data on both use of infliximab plus methotrexate and use of a placebo plus methotrexate. Although individual

biosimilars were not compared in that study, results indicated no major difference in ACR20 response between the pooled biosimilars and infliximab.[29] Similarly, a study by Graudal and colleagues[30] found that the individual treatment effects of infliximab-abda and infliximab-dyyb were comparable to the reference product's in terms of RA progression; however, these biosimilars were not directly compared.

The results of our meta-analysis should be considered in the context of several limitations. Importantly, the network of trials was sparse, with only one study being identified for each of the biosimilars except for infliximab-dyyb, for which 2 studies were identified; this limited the robustness of our evaluation and the indirect comparisons performed. Additionally, while the included studies were all highly similar with regard to methodology and design, follow-up periods differed significantly. Long-term data were available only for infliximab-dyyb and infliximab-abda, which could have impacted the applicability of our findings. To address this limitation, a sensitivity analysis was conducted to evaluate ACR20 response at 30 weeks instead of 54 weeks, which was the follow-up period reported in the 2 longer-term studies. The results of the sensitivity analysis were consistent with findings of the primary efficacy analysis, indicating that follow-up period duration did not greatly impact the results (see eTable 2). Lastly, the primary efficacy analysis focused on only one outcome, ACR20, and assessed only efficacy data from RCTs. Investigators who conduct future network meta-analyses may consider evaluating additional outcomes or incorporating real-world effectiveness data from observational studies.

Conclusion

Results of a network meta-analysis suggest that infliximab biosimilars are generally comparable with regard to ACR20 response and SAEs. In the absence of any meaningful differences in safety or efficacy, cost may be the deciding factor when choosing a biosimilar agent for formulary inclusion.

Disclosures

The authors have declared no potential conflicts of interest.

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Key Points

- Individual biosimilars for the same reference product are generally not directly compared in clinical studies; thus, there may be differences between agents in clinical and safety outcomes.
- The results of a network meta-analysis suggest that infliximab biosimilars are comparable to each other with regard to both the outcomes of 20% improvement in American College of Rheumatology core measures and the rate of serious adverse effects.
- These results may help clinicians, payers, and healthcare organizations make decisions about the choice of an infliximab biosimilar agent; with all other things being equal, product cost and contractual opportunities may become the primary deciding factor.

Table 1. Study Characteristics and Select Results of Included Randomized Controlled Trials

	Genovese et al[24] (2020)	Cohen et al[25] (2018)	Smolen et al[26] (2017)	Yoo et al[27] (2016)	Takeuchi et al[28] (2015)
Design	RCT, DB, MC	RCT, DB, MC	RCT, DB, MC	RCT, DB, MC	RCT, DB, MC
Sample size	558	650	584	606	101
Patient characteristics					
Age, mean, y	54.9	52.8	52.1	50	54.1
Disease duration, mean, y	8.53	6.9	6.4	NR	7.6
Swollen joint count, mean	14.7	16.2	14.7	15.7	12.5
Tender joint count, mean	23.4	25.2	23.8	24.8	16.3
DSA28-CRP, mean	5.59	6	6.5	5.8	5.2
Interventions	INF 3 mg/kg or INF-axxq 3 mg/kg plus MTX[a]	INF 3 mg/kg or INF-qbtx 3 mg/kg plus MTX	INF 3 mg/kg or INF-abda 3 mg/kg plus MTX	INF 3 mg/kg vs INF-dyyb 3 mg/kg plus MTX	INF 3 mg/kg vs INF-dyyb 3 mg/kg plus MTX
Primary efficacy outcome	ACR20	ACR20	ACR20	ACR20	ACR20
Equivalence margin for efficacy[b]	±15%	±13.5%	±15%	±15%	NA[c]
Follow-up period	22 weeks [a]	30 weeks	54 weeks	54 weeks	54 weeks
Efficacy results[d]					
ACR20 with use of biosimilar, %	68.1	67	65.3	60.9	64.0
ACR20 with use of reference product, %	59.1	70.1	69.2	58.6	49.0
ACR20 risk difference, % (CI)	9.37 (2.67-15.96)	–2.28 (–9.69 to 5.13)	–3.07 (–12.00 to 5.86)	2 (–6 to 10)	15 (NR)
Safety results					
Any AE with use of biosimilar, %	51.8	57.3	61.7	60.1	88.2
Any AE with use of reference product, %	49.6	54.0	65.2	60.8	81.1
SAE with use of biosimilar, %	3.2	5.0	10.0	10.0	15.7
SAE with use of reference product, %	5.0	6.1	10.6	7.0	15.1

Abbreviations: ACR20, 20% improvement in American College of Rheumatology core measures; AE, adverse event; CI, confidence interval; DAS28-CRP, disease activity score in 28 joints plus 4 scoring components based on C-reactive protein level; DB, double blind; INF, infliximab; MC, multicenter; MTX, methotrexate; NA, not applicable; NR, not reported; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious adverse event.

[a]At week 22, patients were rerandomized to either continue INF or switch from INF to INF-axxq.

[b]Based on ACR20 response difference between the biosimilar and reference product.

[c]Investigators only tested for significance and reported a *P* value.

[d]As reported by the investigators in the primary publication; values derived from analysis of data for either prespecified per-protocol or intention-to-treat population.

Table 2. League Table of Results of Analysis of ACR20 Response With Use of Infliximab vs Biosimilars[a]

INF	1.202 (0.732-1.974)	0.678 (0.432-1.064)	0.794 (0.539-1.170)	1.156 (0.737-1.815)
0.832 (0.506-1.367)	INF-abda	0.564 (0.288-1.103)	0.661 (0.352-1.241)	0.962 (0.492-1.881)
1.475 (0.940-2.315)	1.773 (0.907-3.466)	INF-axxq	1.172 (0.647-2.123)	1.705 (0.901-3.227)
1.259 (0.854-1.855)	1.513 (0.806-2.840)	0.854 (0.471-1.547)	INF-dyyb	1.456 (0.803-2.638)
0.865 (0.551-1.358)	1.039 (0.532-2.033)	0.586 (0.310-1.109)	0.687 (0.379-1.245)	INF-qbtx

Abbreviations: ACR20, 20% improvement in American College of Rheumatology core measures; INF, infliximab.

[a]All data are odds ratios with 95% confidence intervals. Odds ratios greater than 1 favor the intervention listed in the corresponding row.

Table 3. Tabular Results of Network Rank Test for ACR20 Response

	Treatment				
Rank	**INF**	**INF-abda**	**INF-axxq**	**INF-dyyb**	**INF-qbtx**
Best, %	0.5	1.9	63.4	32.0	2.1
2nd best, %	13.3	8.2	28.6	41.2	8.7
3rd best, %	51.3	14.3	4.8	12.6	16.9
4th best, %	30.1	27.0	2.4	8.9	31.7
Worst, %	4.8	48.5	0.7	5.3	40.7
SUCRA, %	0.4	0.2	0.9	0.7	0.2

Abbreviations: ACR20, 20% improvement in American College of Rheumatology core measures; INF, infliximab; SUCRA, surface under the cumulative ranking curve.

Table 4. League Table of Results of Analysis of Rates of Serious Adverse Effects With Use of Infliximab vs Biosimilars[a]

INF	1.065 (0.624-1.817)	1.585 (0.674-3.725)	0.751 (0.480-1.176)	1.254 (0.638-2.466)
0.939 (0.550-1.603)	INF-abda	1.488 (0.543-4.078)	0.706 (0.351-1.418)	1.178 (0.497-2.788)
0.631 (0.268-1.483)	0.672 (0.245-1.841)	INF-axxq	0.474 (0.181-1.244)	0.791 (0.266-2.352)
1.331 (0.850-2.084)	1.417 (0.705-2.848)	2.110 (0.804-5.537)	INF-dyyb	1.669 (0.741-3.757)
0.797 (0.406-1.568)	0.849 (0.359-2.011)	1.264 (0.425-3.758)	0.599 (0.266-1.349)	INF-qbtx

Abbreviation: INF, infliximab.

[a]All data are odds ratios with 95% confidence intervals. Odds ratios less than 1 favor the intervention listed in the corresponding row.