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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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VIRTUAL CONFERENCE

RhAPP
RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Interpreting Medical Literature

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Disclosure

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Faculty Disclosures

Donald Miller, Pharm.D.

- There are no relationships to disclose.

Objectives

- Following this workshop, the participant will be able to better read clinical research, by being able to explain the following terms:
  - Randomized, controlled study
  - Phase 1, 2, 3 and 4 studies
  - Primary, secondary and surrogate outcomes
  - Intent-to-treat versus per-protocol analyses
  - P values, standard deviation, confidence interval, statistical power, and t tests
  - Incidence rate, relative risk, risk ratio, hazard ratio, and odds ratio
  - Number needed to treat and number needed to harm
  - Systematic review and meta-analysis
  - Post hoc analysis and noninferiority study

Approach and Caveats

- I will be using actual study examples from recent literature to review common terms and concepts that can be confusing in reading literature.
  - I cannot be comprehensive in less than one hour.
  - Explanations will necessarily be simplified and aimed at persons without previous training in evidence-based medicine.
  - Consistent with a workshop format, questions are welcome as we go through the slides.

Safety and Efficacy of Lenabasum in a Phase II, Randomized, Placebo-Controlled Trial in Adults With Systemic Sclerosis

Objective: To assess the safety and efficacy of lenabasum in diffuse cutaneous systemic sclerosis (dcSSc).

Methods: A randomized, double-blind, placebo-controlled, phase II study was conducted at 9 SSc clinics in the US. Adults with dcSSc of ≤6 years' duration who were receiving stable standard-of-care treatment were randomized to receive lenabasum (n = 27) or placebo (n = 15). Lenabasum doses were 5 mg once daily, 20 mg once daily, or 20 mg twice daily for 4 weeks, followed by 20 mg twice daily for 8 weeks. Safety and efficacy were assessed at weeks 4, 8, 12, and 16.

Results: Adverse events (AEs) occurred in 63% of the lenabasum group and 60% of the placebo group, with no serious AEs related to lenabasum. Compared to placebo, lenabasum treatment was associated with greater improvement in the American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score and other efficacy outcome measures that assessed overall disease, skin involvement, and patient-reported function. The median CRISS score increased in the lenabasum group during the study, reaching 0.33, versus 0.00 in the placebo group, at week 16 (P = 0.07 by 2-sided mixed-effects model repeated-measures analysis). Gene expression in inflammation and fibrosis pathways was reduced, and inflammation and fibrosis were improved on histologic evaluation of skin biopsy specimens, in the lenabasum group compared to the placebo group (all $P \leq 0.05$).

Conclusion*:* Despite a short trial duration in a small number of patients in this phase II study in dcSSc, our findings indicate that lenabasum improves efficacy outcomes and underlying disease pathology with a favorable safety profile.

Arthritis & Rheumatology. Vol. 72, No. 8. August 2020. pp 1350–1360. https://doi.org/10.1002/art.41294.

Definitions

- Phase II
  - Clinical studies are typically divided into 4 phases – Phase 1 consists of dose-ranging studies in healthy persons focused on adverse events, phase 2 is short duration trials looking for signs of efficacy at different doses, phase 3 is large scale controlled clinical trials aimed at regulatory approval, and phase 4 is any post-marketing study.
  - This study is a good example of a small (42 patients total) study that looked at multiple doses to test both efficacy and safety in actual patients with dcSSC.
- Randomized, double-blind, placebo controlled
  - Randomized refers to random assignment to an active drug or control group (NOT random sampling). A placebo group is not essential except when trying to prove initial efficacy beyond a placebo effect.
  - Blinding means masking the patient and/or investigator to identity of treatment.
  - The main alternative to a randomized clinical trial (RCT) is an observational design (i.e. give the drug to one or more groups of patients and observe). Why would patients in this or any trial possibly have improved even without treatment?
  - Random assignment to groups is a powerful method of creating similar characteristics in each group – it allows us to control for the effect of confounders.

Observational Studies

- Actually more common than RCTs because they are easier to do, and do not have ethical problems with potentially assigning some persons to an inferior treatment (think early hydroxychloroquine data in Covid-10).
- May also be called cohort studies.
- For example, to look at adverse effects of tobacco use, we can only observe persons who use and do not use the product and then compare.
- But people choose to use or not use products for various reasons and therefore the groups are not very comparable (the comparisons are confounded by additional variables). Thus observational studies cannot prove causality.

Definitions

- Primary/Secondary Outcomes – The primary outcome is the one key outcome which determines success of the product in a study. This is often one of the ACR composite criteria (in this case CRISS score). Secondary outcomes are additional outcomes that are relevant but considered less important than the primary outcome (gene expression, skin histology).
- Surrogate Markers – intermediate outcomes that stand in for a primary outcome that is difficult to measure or would take too much time to develop. In short term studies there may not be enough time for many patients to reach the preferred measure. (Think vaccines – immune response vs. preventing infection).

Results of a 6-Week Treatment With 10 mg Prednisolone in Patients With Hand Osteoarthritis (HOPE): A Double-Blind, Randomised, Placebo-Controlled Trial

We randomly assigned 46 (50%) patients to receive prednisolone and 46 (50%) patients to receive placebo, all of whom were included in the modified intention-to-treat analysis of the primary endpoint. 42 (91%) patients in the prednisolone group and 42 (91%) in the placebo group completed the 14-week study. The mean change between baseline and week 6 on VAS-reported finger pain was -21·5 (SD 21·7) in the prednisolone group and -5·2 (24·3) in the placebo group, with a mean between-group difference (of prednisolone vs placebo) of -16·5 (95% CI -26·1 to -6·9; p=0·0007).

Lancet. 2019;394(Nov 30):1993-2001. doi: 10.1016/S0140-6736(19)32489-4.

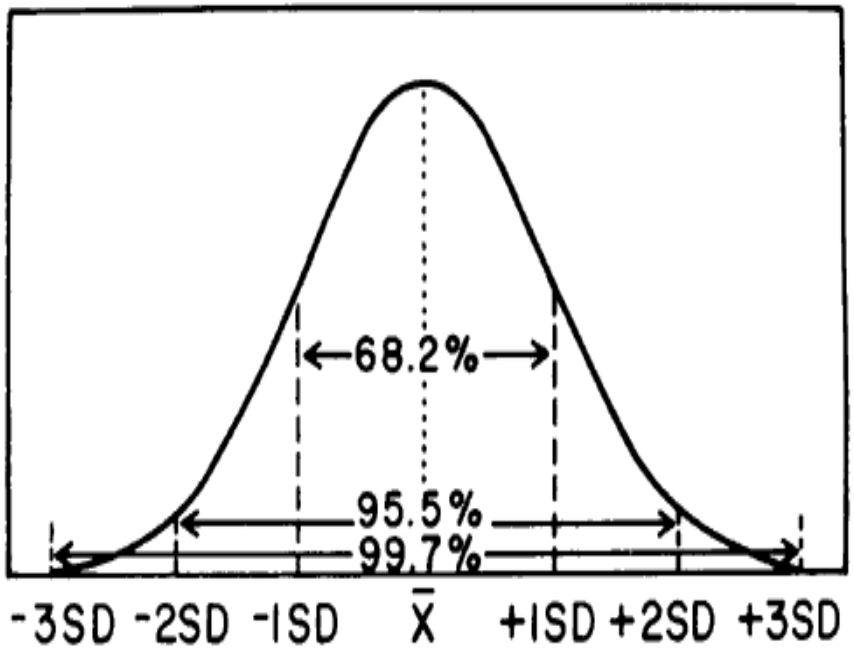
Definitions

- Analysis of most studies can be done in 2 ways – as a per-protocol analysis OR as an intent-to-treat (ITT) analysis.
- Per-protocol means analyzing only patients who completed the entire study and followed all the rules of the study protocol. This is best to find out how a drug works in ideal conditions. However, it is not very realistic to everyday use where most patients lack perfect adherence to drugs, and may stop early for various reasons.
- Intent-to-treat means analyzing ALL patients who were randomized to a treatment group, regardless of compliance or ability to finish the study. This analysis simulates the outcomes we would expect in real life.

- The differences in analyses can be illustrated by considering an example. Perhaps 40 patients start taking a drug for RA, 20 drop out before the end of the study due to adverse effects and 20 complete a full 3 month trial. If we consider only the finishers we may find that 16 of 20 successfully had an ACR50 response. Thus efficacy under optimal circumstances (per-protocol) is 80%. But if we do intent to treat analysis, only 16 of 40 patients, or 40% success was achieved. In the intent to treat analysis we appropriately accounted for the high rate of drop-outs from adverse effects or difficulty in compliance.
- ITT analyses are preferred because of their practical relevance, but per-protocol analyses are still useful, especially in early pharmacology studies. But as readers, it is important to know the difference! (The difference in results is more dramatic as drop-out rate increases).

Definitions – Mean and Standard Deviation

- 68% of observations lie within one SD of the mean
- 95% of observations lie within two SD of the mean
- 99.7% of observations lie within three SD of the mean



Fenebrutinib Versus Placebo or Adalimumab in Rheumatoid Arthritis: A Randomized, Double-Blind, Phase II Trial

Objective

- To evaluate fenebrutinib, an oral and highly selective noncovalent inhibitor of Bruton's tyrosine kinase (BTK), in patients with active rheumatoid arthritis (RA).

Methods

- Patients with RA and an inadequate response to methotrexate (MTX) (cohort 1; n = 480) were randomized to receive fenebrutinib (50 mg once daily, 150 mg once daily, or 200 mg twice daily), adalimumab (40 mg every other week), or placebo. Patients with RA and an inadequate response to tumor necrosis factor inhibitors (cohort 2; n = 98) received fenebrutinib (200 mg twice daily) or placebo. Both cohorts continued MTX therapy.

Arthritis & Rheumatology. Vol. 72, No. 9, September 2020. pp 1435–1446. https://doi.org/10.1002/art.41275.

Fenibrutinib Continued…

Results

- In cohort 1, the percentages of patients in whom American College of Rheumatology 50% improvement criteria (ACR50) was achieved at week 12 were similar in the fenebrutinib 50 mg once daily and placebo groups, and were higher in the fenebrutinib 150 mg once daily group (28%) and 200 mg twice daily group (35%) than in the placebo group (15%) (*P* = 0.016 and *P* = 0.0003, respectively). Fenebrutinib 200 mg twice daily and adalimumab (36%) were comparable (*P* = 0.81). In cohort 2, ACR50 was achieved in more patients receiving fenebrutinib 200 mg twice daily (25%) than placebo (12%) (*P* = 0.072). The most common adverse events in the fenebrutinib groups included nausea, headache, anemia, and upper respiratory tract infections. Fenebrutinib had significant effects on myeloid and B cell biomarkers (CCL4 and rheumatoid factor). Fenebrutinib and adalimumab caused overlapping as well as distinct changes in B cell and myeloid biomarkers.

Conclusion

- Fenebrutinib demonstrates efficacy comparable to adalimumab in patients with an inadequate response to MTX, and safety consistent with existing immunomodulatory therapies for RA. These data support targeting both B and myeloid cells via this novel mechanism for potential efficacy in the treatment of RA.

Definitions

- P values – the Probability of an observed result of that size or larger occurring by chance alone. Events occurring spontaneously less than 5% of the time are considered rare and thus more likely to be reproducible and NOT due to chance alone.
- Of note, a statistically significant result can occur due to effect of the intervention OR due to any of many confounding factors (e.g. placebo effect and other confounders). Statistics only deal with the role of chance.
- Even a result with a low p value MAY have occurred by chance alone; it is just unlikely.
- There is no good or bad p value. Fenebrutinib 200 mg bid and adalimumab had similar responses (35 vs 36%), so a p = 0.81 is to be expected.
- Calculation of p values – depends on the characteristics of the data we are analyzing. See upcoming slides.

Uncertainty of an Estimate

- Any study will give results that are true for the group studied. But we are really concerned with making an inference, or extrapolation, to the entire population the patients were drawn from. Due to the role of chance and random variation in our sample, we need to hedge our conclusions by incorporating some indicator of uncertainty in our estimate. Usually, in addition to the p value, this is done with a confidence interval.

Definitions – Confidence Interval

- One can calculate a zone of confidence that quantifies uncertainty for any finding. We can calculate a zone of 95% confidence or anything greater or smaller. This is also called the margin of error in election polls.
- When estimating a mean for a population we can take the standard deviation and divide by the square root of the sample size (N) to get the standard error. This gives us some idea of how reliable our estimate of the mean is. More specifically, 2 standard errors on either side of the mean gives us a 95% confidence interval.
- Assume we want to know the average systolic BP of rheumatology health professionals. We take a sample of 100 persons to measure and find an average SBP of 135 with SD of 10. Those statistics tell a lot about our sample. But it also allows us to infer the mean SBP of similar persons.
- The SE is 10/square root of 100 = 1.
  The 95% CI is 135 ± 2 = 133 to 137.

Comparative Study of Real-Life Management Strategies in Gout: Data From Two Protocolized Gout Clinics

Objective: To compare outcomes of 2 gout clinics that implemented different treatment strategies.

Methods: Patients newly diagnosed with gout and a follow-up of 9–15 months were included. Co-primary outcomes were the proportion of patients reaching a serum uric acid (UA) ≤0.36 mmoles/liter and free of flares. Secondary outcomes were the proportion of patients requiring treatment intensification and experiencing adverse events. One clinic adopted a strict serum UA (≤0.30 mmoles/liter target) strategy, with early addition of a uricosuric to allopurinol, and the other clinic adopted a patient-centered (PC) strategy emphasizing a shared decision based on serum UA and patient satisfaction with gout control. Independent *t*-tests or chi-square tests were used to test differences in outcomes, and logistic regressions were used to adjust the effect of the treatment center on outcomes for confounders.

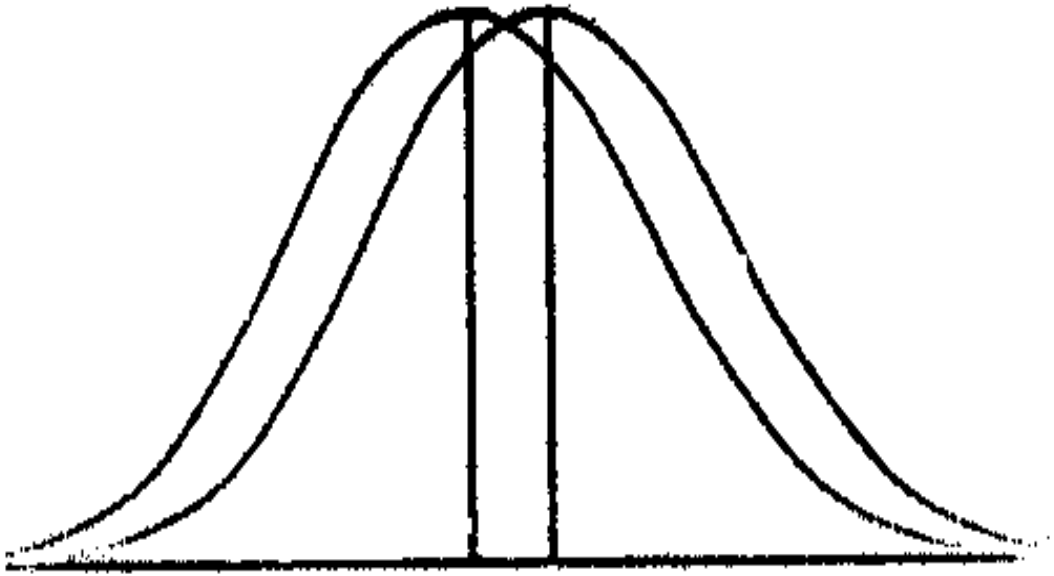
Results: In total, 126 and 86 patients had a follow-up mean ± SD of 11.3 ± 1.8 versus 11.1 ± 1.9 months. In the UA strategy, 105 of 126 patients (83%) compared to 63 of 86 (74%) in the PC strategy ($P = 0.10$) reached the threshold of ≤0.36 mmoles/liter; and 58 of 126 (46%) versus 31 of 86 (36%) were free of flares ($P = 0.15$). In the UA strategy, 76 of 126 patients (60%) were on allopurinol monotherapy compared to 63 of 86 (73%) in the PC strategy ($P = 0.05$), yet the number of adverse events was not different (n = 25 [20%] versus n = 20 [23%]; $P = 0.55$). Adjusting for confounders did not substantially change these associations.

Conclusion: A strict UA strategy resulted in a nonsignificantly higher proportion of patients reaching a serum UA ≤ 0.36 mmoles/liter and being free of flares. This result was accomplished with significantly more therapy intensification. The small sample size plays a role in the significance of results.

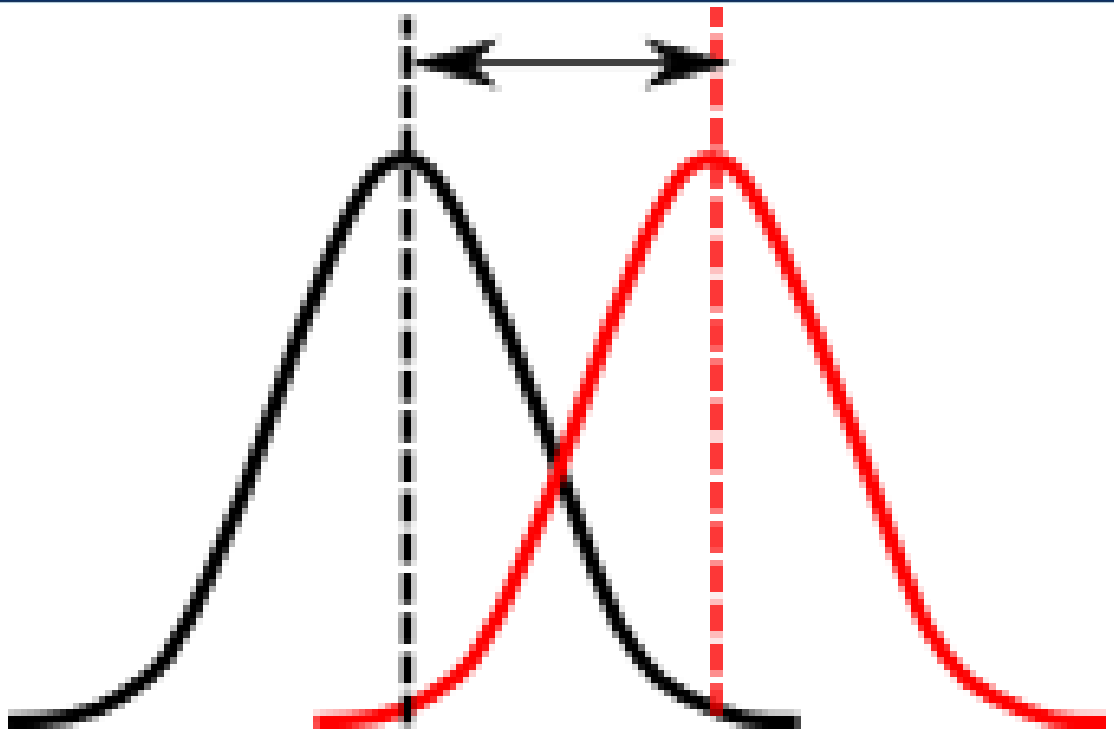
Arthritis Care & Research. Vol. 72, No. 8. August 2020. 1169–117. https://doi.org/10.1002/acr.23995.

Definitions

- Power in statistics – a p value is very dependent on sample size. A difference of any size can be statistically significant when the sample sizes are large. Likewise the 95% confidence interval will be small. On the other hand, even large differences will NOT be statistically significant when sample sizes are small.



T-tests look at how far the means of 2 groups are from each other in relation to the variability of the distributions



Some Analyses Use Frequencies, Regressions

- If we are comparing simple frequencies of events (e.g. how often we reached desired uric acid threshold) then we must use statistical tests that compare observed frequencies to those under the null hypothesis. These include chi-square and Fisher's Exact test.
- Correlation and regression are techniques used to explain how sets of data are related to each other. Multiple regression techniques (like logistic regression here) are very useful in teasing out and eliminating the effects of confounding variables (e.g. demographic differences or concomitant drug therapies)

Association Between Oral Corticosteroid Bursts and Severe Adverse Events: A Nationwide Population-Based Cohort Study

Objective: To examine the associations between steroid bursts and severe adverse events, specifically gastrointestinal (GI) bleeding, sepsis, and heart failure.

Design: Self-controlled case series.

Setting: Entire National Health Insurance Research Database of medical claims records in Taiwan.

Participants: Adults aged 20 to 64 years with continuous enrollment in the National Health Insurance program from 1 January 2013 to 31 December 2015.

Measurements: Incidence rates of severe adverse events in steroid burst users and non–steroid users, as well as incidence rate ratios (IRRs) for severe adverse events within 5 to 30 and 31 to 90 days after initiation of steroid therapy.

Results: Of 15 859 129 adult participants, 2 623 327 who received a single steroid burst were included. The most common indications were skin disorders and respiratory tract infections. **The incidence rates per 1000 person-years in steroid bursts were 27.1 (95% CI, 26.7 to 27.5) for GI bleeding, 1.5 (CI, 1.4 to 1.6) for sepsis, and 1.3 (CI, 1.2 to 1.4) for heart failure. Rates of GI bleeding (IRR, 1.80 [CI, 1.75 to 1.84]), sepsis (IRR, 1.99 [CI, 1.70 to 2.32]), and heart failure (IRR, 2.37 [CI, 2.13 to 2.63])** significantly increased within 5 to 30 days after steroid therapy initiation and attenuated during the subsequent 31 to 90 days.

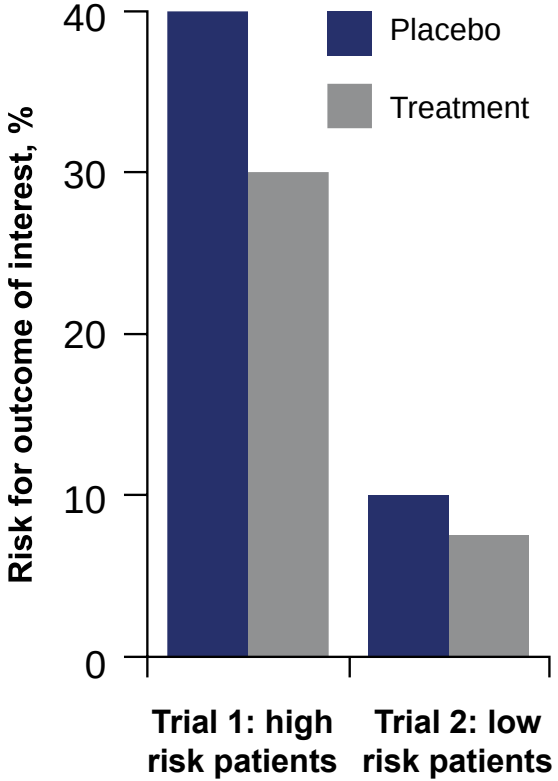
Conclusion: Oral corticosteroid bursts are frequently prescribed in the general adult population in Taiwan. The highest rates of GI bleeding, sepsis, and heart failure occurred within the first month after initiation of steroid therapy.

Ann Intern Med. 2020;173:325-330. https://doi.org/10.7326/M20-0432.

Association Between Oral Corticosteroid Bursts and Severe Adverse Events: A Nationwide Population-Based Cohort Study

Study design was observational (retrospective cohort) but confounding for lifestyle and co-morbidity risk factors was reduced by using a self-controlled approach (comparing adverse event rates 5-90 days before and after within the same person).

Incidence rate (also known as absolute risk) is simply the observed incidence of an event (e.g. 27.1/1000 persons per year for GI bleeding on steroids). Incidence rate ratio (also known as relative risk) is the ratio of incidence with and without drug exposure (e.g. 1.80 for GI bleeding). Thus baseline risk without steroids was 15/1000, since 27.1/15 = 1.80.



- New drug for lupus nephritis to reduce mortality
- First studied in high risk population
  - 40% baseline risk of death
  - 30% mortality among treated
  - Later studied in a lower risk population:
    - 10% mortality rate among untreated
    - 7.5% mortality among treated
  - How would you describe the effect of the new drug?

Interpreting Frequency Data

- Relative Risk – simple ratio of frequencies (describe relative risk reduction or increase)
- Absolute risk change – more important, the change in incidence in absolute terms

Mediterranean Diet and Risk of Rheumatoid Arthritis: A Population-Based Case-Control Study

Methods: Data on 1721 patients with incident RA (cases) and 3667 controls, matched on age, gender and residential area, from the Swedish epidemiological investigation of RA (EIRA), a population-based case-control study, were analysed using conditional logistic regression. The Mediterranean diet score, ranging from 0 to 9, was calculated from a 124-item food frequency questionnaire.

Results: In the EIRA study (median age of participants 53 years), 24.1% of the patients and 28.2% of the controls had high adherence to the Mediterranean diet (a score between 6 and 9). After adjustments for body mass index, educational level, physical activity, use of dietary supplements, energy intake, and smoking, high adherence reduced the odds of developing RA by 21% (OR 0.79; 95% CI 0.65-0.96) as compared to low adherence (a score between 0 and 2). The OR was even lower among men (OR 0.49; 95% CI 0.33-0.73), but no significant association was found among women (OR 0.94; 95% CI 0.74-1.18). An association between high diet score and low risk of RA was observed in rheumatoid factor (RF)-positive (OR 0.69; 95% CI 0.54-0.88), but not RF-negative RA (OR 0.96; 95% CI 0.68-1.34), and in RA characterised by presence of antibodies to citrullinated peptides (ACPA), but not in ACPA-negative RA.

Conclusions: In this large population-based case-control study, the Mediterranean diet score was inversely associated with risk of RA. However, an association was only found among men and only in seropositive RA.

Arth Res Ther. 2018;20: Article 175. https://doi.org/10.1186/s13075-018-1680-2.

Definitions

- Case-Control Study
  - Case-control studies follow groups as formed by outcome, not exposure. They start with a sample of cases, who have the disease, and controls, who don't have it, back in time to identify potential causes by contrasting past characteristics of cases and controls. In a case-control design, the comparison is between people who have a disorder and people who don’t, while a cohort design compares people exposed to a drug or risk factor with those not exposed.
  - This approach cannot determine the true incidence of a disease or absolute risk from exposure to something because there is no starting cohort. Thus an alternate estimate of risk in epidemiologic studies is the odds ratio (relative odds of exposure), which conveniently does not require us to know true incidence.

Definitions

- Odds Ratio – *Estimates* relative risk when case-control data are used. In this case high adherence to a Mediterranean diet reduced the risk of developing RA (OR 0.79; 95% CI 0.65-0.96) as compared to low adherence. We could also say the Mediterranean diet reduced risk of RA by 21%, or that your relative risk of developing RA is only 79% compared to persons ingesting other diets.
- Post Hoc Analysis – An analysis that was not planned but done because it seemed interesting or relevant (e.g. a subgroup analysis of females, elderly, RF-positive patients only, etc.). These can be falsely positive (significant) because they were done AFTER peeking at the data and driven by bias or unexpected data.

Tumor Necrosis Factor Alpha Drugs in Rheumatoid Arthritis: Systematic Review and Meta-Analysis of Efficacy and Safety

Background: To analyse available evidence on the efficacy and safety of anti-TNFalpha drugs (infliximab, etanercept and adalimumab) for treating rheumatoid arthritis (RA).

Methods: We searched systematically for randomized controlled clinical trials on treatment of RA with anti-TNFalpha drugs, followed by a systematic review with meta-analysis. Trials were searched from MEDLINE, EMBASE and Cochrane Library databases. The American College of Rheumatology (ACR) efficacy response criteria were used. Safety parameters provided by the trials were also assessed. Positive and undesired effects were estimated using combined relative risks (RR), number needed to treat (NNT) and number needed to harm (NNH). Heterogeneity was evaluated by Cochrane's Q and I2 statistics.

BMC Musculoskelet Disord. 2008;9:52. doi: 10.1186/1471-2474-9-52.

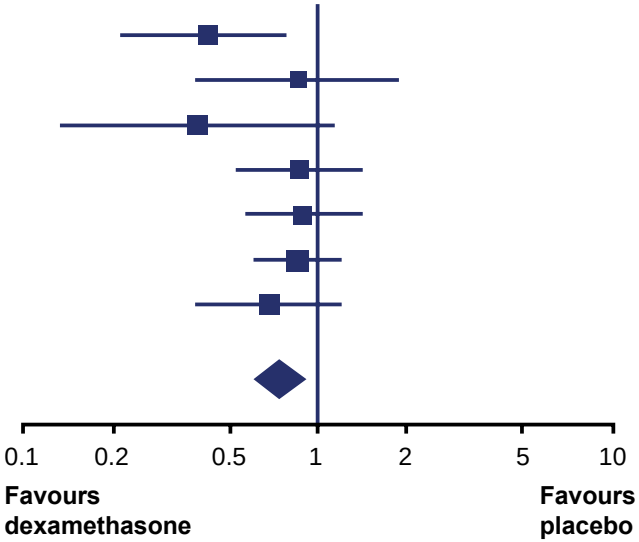
Definitions

- Systematic review and meta-analysis
  - A systematic review is literature review done via one or more databases that is structured to include all articles meeting certain criteria (as opposed to a narrative review that may be more subjective in the articles included).
  - A meta-analysis is a review article in which authors take previous independent research studies and combine them through mathematical techniques to get an overall estimate of drug effect.

Study	No with recurrent headache/No in group: Dexamethasone group	No with recurrent headache/No in group: Placebo group	Relative risk (fixed) (95% CI)	Weight (%)	Relative risk (fixed) (95% CI)
Innes 1999	9/49	22/49		14.97	0.41 (0.21 to 0.80)
Jones 2003	8/34	10/36		6.61	0.85 (0.38 to 1.89)
Baden 2006	4/31	8/24		6.14	0.39 (0.13 to 1.13)
Donaldson 2006	21/57	18/42		14.10	0.86 (0.53 to 1.40)
Fiesseler 2006	19/44	20/41		14.09	0.89 (0.56 to 1.40)
Friedman 2007	39/106	43/99		30.26	0.85 (0.61 to 1.19)
Rowe 2007	14/64	20/62		13.83	0.68 (0.38 to 1.22)
Total (95% CI)	385	353		100.00	0.74 (0.60 to 0.90)

Test for heterogeneity: $\chi^2 = 6.21$, df = 6, P = 0.40, $I^2 = 3.4\%$

Test for overall effect: z = 3.01, P = 0.003



Tumor Necrosis Factor Alpha Drugs in Rheumatoid Arthritis: Systematic Review and Meta-Analysis of Efficacy and Safety

Results: Thirteen trials (7087 patients) met the inclusion criteria. The combined RR to achieve a therapeutic response to treatment with recommended doses of any anti-TNFalpha drug was 1.81 (95% CI 1.43-2.29) with a NNT of 5 (5-6) for ACR20. NNT for ACR50 [5 (5-6)] and ACR70 [7 (7-9)] were similar. Overall therapeutic effects were also similar regardless of the specific anti-TNFalpha drug used and when higher than recommended doses were administered. However, lower than recommended doses elicited low ACR70 responses (NNT 15). Comparison of anti-TNFalpha drugs plus methotrexate (MTX) with MTX alone in patients with insufficient prior responses to MTX showed NNT values of 3 for ACR20, 4 for ACR50 and 8 for ACR70. Comparison of anti-TNFalpha drugs with placebo showed a similar pattern. Comparisons of anti-TNFalpha drugs plus MTX with MTX alone in patients with no previous resistance to MTX showed somewhat lower effects. Etanercept and adalimumab administered as monotherapy showed effects similar to those of MTX. Side effects were more common among patients receiving anti-TNFalpha drugs than controls (overall combined NNH 27). Patients receiving infliximab were more likely to drop out because of side effects (NNH 24) and to suffer severe side effects (NNH 31), infections (NNH 10) and infusion reactions (NNH 9). Patients receiving adalimumab were also more likely to drop out because of side effects (NNH 47) and to suffer injection site reactions (NNH 22). Patients receiving etanercept were less likely to drop out because of side effects (NNH for control versus etanercept 26) but more likely to experience injection site reactions (NNH 5).

BMC Musculoskelet Disord. 2008;9:52. doi: 10.1186/1471-2474-9-52.

Definitions

- NNT (number needed to treat) is the number of persons who must receive an intervention to obtain a certain outcome (e.g. reaching ACR 50 response versus absolute improvement). Only relevant when the outcome is dichotomized to response/no response. We need this number because not all persons respond to any drug or intervention (if that did occur the NNT would be 1).
- For example if 25% of patients have an ACR50 response the number needed to treat to obtain that response is 1/0.25 = 4.
- Number needed to harm is calculated the same way, except it describes an adverse event.

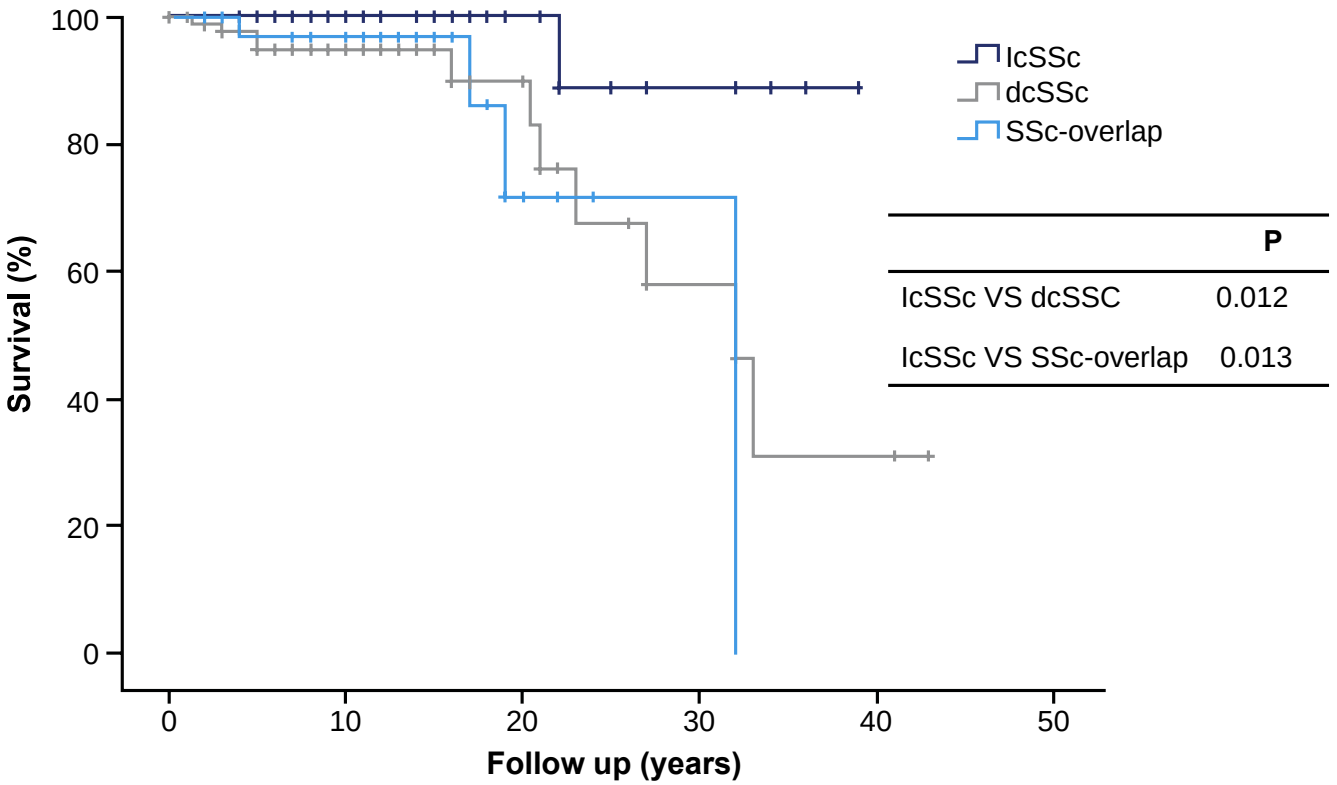
Survival Rate, Causes of Death, and Risk Factors in Systemic Sclerosis: A Large Cohort Study

To investigate the clinical pattern, survival rate, causes of death and risk factors in a large cohort of Chinese Han patients with systemic sclerosis (SSc). Inpatients treated from 2002 to 2014 were included in this study. Patients were classified into diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), and SSc-overlap syndrome groups.

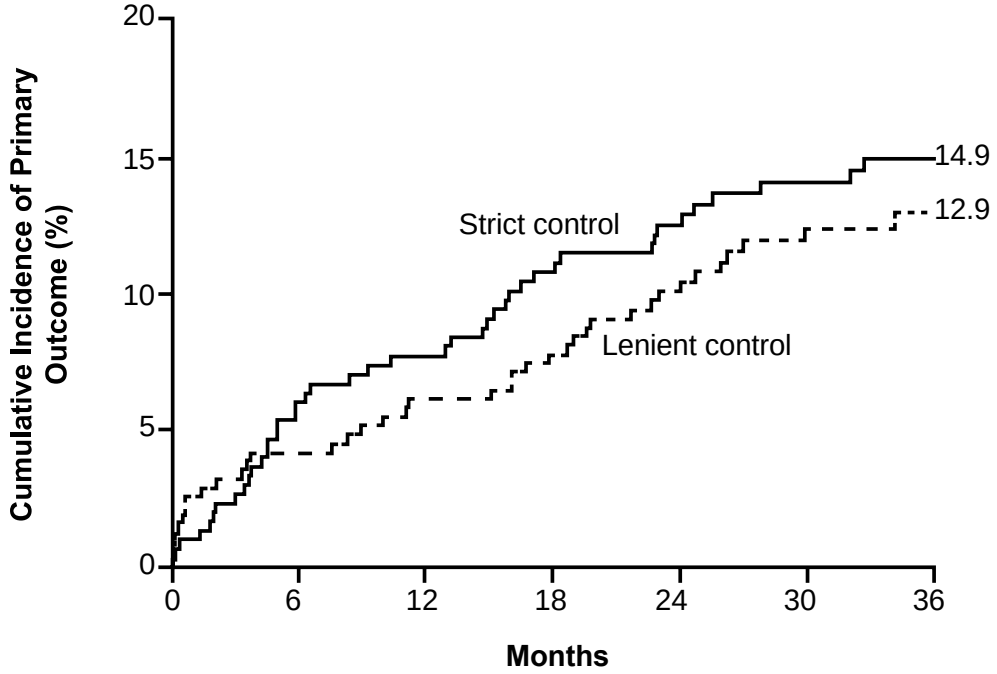
The overall survival rates were 98% and 95% at 5 and 10 years, respectively. The overall standard mortality ratio (SMR) was 2.22. The most common cause of death was ILD combined with infection (8/16, 50%), followed by kidney failure (2/16, 12.5%). On crude analysis, pulmonary hypertension, ILD, cardiac involvements, renal involvements, and digital ischemia were associated with poor prognosis. On multivariate analysis, pericardial effusion ($p = 0.000$) and digital ischemia ($p = 0.016$) were independent prognostic factors of death.

The mortality rate of patients with SSc is mildly increased in comparison with the general population. ILD is the most common systemic involvement and the principal cause of death in SSc. Pericardial effusion and digital ischemia are independent factors associated with death.

Clinical Rheumatol. 2018;37:3051-3056. https://doi.org/10.1007/s10067-018-4291-z.



	P
lcSSc VS dcSSC	0.012
lcSSc VS SSc-overlap	0.013



No. at Risk							
Strict control	303	282	273	262	246	212	131
Lenient control	311	298	290	285	255	218	138

Interpreting Survival Analyses

- The comparative risk of the outcome is usually described by the Hazard Ratio – which is interpreted like a relative risk but is calculated over the entire follow-up period, not just at the end of the study.
- In this case they used the Standard Mortality Ratio (SMR), which is the ratio of observed deaths in the study group to expected deaths in the general population. This was done to compare the SSC groups to a standard of some kind.

More Definitions

- Non-inferiority
  - Traditionally, we want to see if an intervention is better (superior) to placebo. But in comparative effectiveness studies we may be satisfied if one treatment is similar to (non-inferior) to a gold standard treatment. For example, a biosimilar drug is just fine if it is as good as the standard; we don't expect it to be superior to the innovator. A low drug dose may just as good as a high dose but surely is not more effective.
  - Proving non-inferiority is a little tricky however, because several quality controls must be included in such studies, most important being large enough in enrollment (having sufficient power to detect a difference).

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Questions?