The Big Four Bulletin
19 September 2018 No. 604

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BMJ (15 September 2018, Vol. 362, No. 8167)

Compliance with requirement to report results on the EU Clinical Trials Register: Cohort study and web resource
Ben Goldacre, Nicholas J DeVito, Carl Heneghan, et al.
BMJ 2018; 362 (Published 12 September 2018)
https://www.bmj.com/content/362/bmj.k3218

Abstract
Objectives To ascertain compliance rates with the European Commission's requirement that all trials on the EU Clinical Trials Register (EUCTR) post results to the registry within 12 months of completion (final compliance date 21 December 2016); to identify features associated with non-compliance; to rank sponsors by compliance; and to build a tool for live ongoing audit of compliance.
Design Retrospective cohort study.
Setting EUCTR.
Participants 7274 of 11 531 trials listed as completed on EUCTR and where results could be established as due.
Main outcome measure Publication of results on EUCTR.
Results Of 7274 trials where results were due, 49.5% (95% confidence interval 48.4% to 50.7%) reported results. Trials with a commercial sponsor were substantially more likely to post results than those with a non-commercial sponsor (68.1% *v* 11.0%, adjusted odds ratio 23.2, 95% confidence interval 19.2 to 28.2); as were trials by a sponsor who conducted a large number of trials (77.9% *v* 18.4%, adjusted odds ratio 18.4, 15.3 to 22.1). More recent trials were more likely to report results (per year odds ratio 1.05, 95% confidence interval 1.03 to 1.07). Extensive evidence was found of errors, omissions, and contradictory entries in EUCTR data that prevented ascertainment of compliance for some trials.
Conclusions Compliance with the European Commission requirement for all trials to post results on to the EUCTR within 12 months of completion has been poor, with half of all trials non-compliant. EU registry data commonly contain inconsistencies that might prevent even regulators assessing compliance. Accessible and timely information on the compliance status of each individual trial and sponsor may help to improve reporting rates.

Intensification of older adults' outpatient blood pressure treatment at hospital discharge: National retrospective cohort study

Timothy S Anderson, Charlie M Wray, Bocheng Jing, et al.
BMJ 2018; 362 (Published 12 September 2018)
https://www.bmj.com/content/362/bmj.k3503

Abstract
Objectives To assess how often older adults admitted to hospital for common non-cardiac conditions were discharged with intensified antihypertensive treatment, and to identify markers of appropriateness for these intensifications.
Design Retrospective cohort study.
Setting US Veterans Administration Health System.
Participants Patients aged 65 years or over with hypertension admitted to hospital with non-cardiac conditions between 2011 and 2013.
Main outcome measures Intensification of antihypertensive treatment, defined as receiving a new or higher dose antihypertensive agent at discharge compared with drugs used before admission. Hierarchical logistic regression analyses were used to control for characteristics of patients and hospitals.
Results Among 14 915 older adults (median age 76, interquartile range 69-84), 9636 (65%) had well controlled outpatient blood pressure before hospital admission. Overall, 2074 (14%) patients were discharged with intensified antihypertensive treatment, more than half of whom (1082) had well controlled blood pressure before admission. After adjustment for potential confounders, elevated inpatient blood pressure was strongly associated with being discharged on intensified antihypertensive regimens. Among patients with previously well controlled outpatient blood pressure, 8% (95% confidence interval 7% to 9%) of patients without elevated inpatient blood pressure, 24% (21% to 26%) of patients with moderately elevated inpatient blood pressure, and 40% (34% to 46%) of patients with severely elevated inpatient blood pressure were discharged with intensified antihypertensive regimens. No differences were seen in rates of intensification among patients least likely to benefit from tight blood pressure control (limited life expectancy, dementia, or metastatic malignancy), nor in those most likely to benefit (history of myocardial infarction, cerebrovascular disease, or renal disease).
Conclusions One in seven older adults admitted to hospital for common non-cardiac conditions were discharged with intensified antihypertensive treatment. More than half of intensifications occurred in patients with previously well controlled outpatient blood pressure. More attention is needed to reduce potentially harmful overtreatment of blood pressure as older adults transition from hospital to home.

Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): Double blind, phase III, randomised controlled, international, multicentre trial

Shi Wu Wen, Ruth Rennicks White, Natalie Rybak, et al. on behalf of the FACT Collaborating Group
BMJ 2018; 362 (Published 12 September 2018)
https://www.bmj.com/content/362/bmj.k3478

Abstract
Objective To determine the efficacy of high dose folic acid supplementation for prevention of pre-eclampsia in women with at least one risk factor: pre-existing hypertension, prepregnancy diabetes (type 1 or 2), twin pregnancy, pre-eclampsia in a previous pregnancy, or body mass index ≥35.
Design Randomised, phase III, double blinded international, multicentre clinical trial.

Setting 70 obstetrical centres in five countries (Argentina, Australia, Canada, Jamaica, and UK).
Participants 2464 pregnant women with at least one high risk factor for pre-eclampsia were randomised between 2011 and 2015 (1144 to the folic acid group and 1157 to the placebo group); 2301 were included in the intention to treat analyses.
Intervention Eligible women were randomised to receive either daily high dose folic acid (four 1.0 mg oral tablets) or placebo from eight weeks of gestation to the end of week 16 of gestation until delivery. Clinicians, participants, adjudicators, and study staff were masked to study treatment allocation.
Main outcome measure The primary outcome was pre-eclampsia, defined as hypertension presenting after 20 weeks' gestation with major proteinuria or HELLP syndrome (haemolysis, elevated liver enzymes, low platelets).
Results Pre-eclampsia occurred in 169/1144 (14.8%) women in the folic acid group and 156/1157 (13.5%) in the placebo group (relative risk 1.10, 95% confidence interval 0.90 to 1.34; P=0.37). There was no evidence of differences between the groups for any other adverse maternal or neonatal outcomes.
Conclusion Supplementation with 4.0 mg/day folic acid beyond the first trimester does not prevent pre-eclampsia in women at high risk for this condition.

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JAMA: Journal of the American Medical Association (18 September 2018, Vol. 320, No. 11)

Association of Clinical Specialty With Symptoms of Burnout and Career Choice Regret Among US Resident Physicians
Liselotte N. Dyrbye, Sara E. Burke, Rachel R. Hardeman, et al.
JAMA. 2018; 320 (11): 1114-1130.
https://jamanetwork.com/journals/jama/article-abstract/2702870

Abstract
Importance Burnout among physicians is common and has been associated with medical errors and lapses in professionalism. It is unknown whether rates for symptoms of burnout among resident physicians vary by clinical specialty and if individual factors measured during medical school relate to the risk of burnout and career choice regret during residency.
Objective To explore factors associated with symptoms of burnout and career choice regret during residency.
Design, Setting, and Participants Prospective cohort study of 4732 US resident physicians. First-year medical students were enrolled between October 2010 and January 2011 and completed the baseline questionnaire. Participants were invited to respond to 2 questionnaires; one during year 4 of medical school (January-March 2014) and the other during the second year of residency (spring of 2016). The last follow-up was on July 31, 2016.
Exposures Clinical specialty, demographic characteristics, educational debt, US Medical Licensing Examination Step 1 score, and reported levels of anxiety, empathy, and social support during medical school.
Main Outcomes and Measures Prevalence during second year of residency of reported symptoms of burnout measured by 2 single-item measures (adapted from the Maslach Burnout Inventory) and an additional item that evaluated career choice regret (defined as

whether, if able to revisit career choice, the resident would choose to become a physician again).

Results Among 4696 resident physicians, 3588 (76.4%) completed the questionnaire during the second year of residency (median age, 29 [interquartile range, 28.0-31.0] years in 2016; 1822 [50.9%] were women). Symptoms of burnout were reported by 1615 of 3574 resident physicians (45.2%; 95% CI, 43.6% to 46.8%). Career choice regret was reported by 502 of 3571 resident physicians (14.1%; 95% CI, 12.9% to 15.2%). In a multivariable analysis, training in urology, neurology, emergency medicine, and general surgery were associated with higher relative risks (RRs) of reported symptoms of burnout (range of RRs, 1.24 to 1.48) relative to training in internal medicine. Characteristics associated with higher risk of reported symptoms of burnout included female sex (RR, 1.17 [95% CI, 1.07 to 1.28]; risk difference [RD], 7.2% [95% CI, 3.1% to 11.3%]) and higher reported levels of anxiety during medical school (RR, 1.08 per 1-point increase [95% CI, 1.06 to 1.11]; RD, 1.8% per 1-point increase [95% CI, 1.6% to 2.0%]). A higher reported level of empathy during medical school was associated with a lower risk of reported symptoms of burnout during residency (RR, 0.99 per 1-point increase [95% CI, 0.99 to 0.99]; RD, −0.5% per 1-point increase [95% CI, −0.6% to −0.3%]). Reported symptoms of burnout (RR, 3.20 [95% CI, 2.58 to 3.82]; RD, 15.0% [95% CI, 12.8% to 17.3%]) and clinical specialty (range of RRs, 1.66 to 2.60) were both significantly associated with career choice regret.

Conclusions and Relevance Among US resident physicians, symptoms of burnout and career choice regret were prevalent, but varied substantially by clinical specialty. Further research is needed to better understand these differences and to address these issues.

Prevalence of Burnout Among Physicians: A Systematic Review

Lisa S. Rotenstein, Matthew Torre, Marco A. Ramos, et al.
JAMA. 2018; 20 (11): 1131-1150
https://jamanetwork.com/journals/jama/article-abstract/2702871

Abstract

Importance Burnout is a self-reported job-related syndrome increasingly recognized as a critical factor affecting physicians and their patients. An accurate estimate of burnout prevalence among physicians would have important health policy implications, but the overall prevalence is unknown.

Objective To characterize the methods used to assess burnout and provide an estimate of the prevalence of physician burnout.

Data Sources and Study Selection Systematic search of EMBASE, ERIC, MEDLINE/PubMed, psycARTICLES, and psycINFO for studies on the prevalence of burnout in practicing physicians (ie, excluding physicians in training) published before June 1, 2018.

Data Extraction and Synthesis Burnout prevalence and study characteristics were extracted independently by 3 investigators. Although meta-analytic pooling was planned, variation in study designs and burnout ascertainment methods, as well as statistical heterogeneity, made quantitative pooling inappropriate. Therefore, studies were summarized descriptively and assessed qualitatively.

Main Outcomes and Measures Point or period prevalence of burnout assessed by questionnaire.

Results Burnout prevalence data were extracted from 182 studies involving 109 628 individuals in 45 countries published between 1991 and 2018. In all, 85.7% (156/182) of studies used a version of the Maslach Burnout Inventory (MBI) to assess burnout. Studies variably reported prevalence estimates of overall burnout or burnout subcomponents:

67.0% (122/182) on overall burnout, 72.0% (131/182) on emotional exhaustion, 68.1% (124/182) on depersonalization, and 63.2% (115/182) on low personal accomplishment. Studies used at least 142 unique definitions for meeting overall burnout or burnout subscale criteria, indicating substantial disagreement in the literature on what constituted burnout. Studies variably defined burnout based on predefined cutoff scores or sample quantiles and used markedly different cutoff definitions. Among studies using instruments based on the MBI, there were at least 47 distinct definitions of overall burnout prevalence and 29, 26, and 26 definitions of emotional exhaustion, depersonalization, and low personal accomplishment prevalence, respectively. Overall burnout prevalence ranged from 0% to 80.5%. Emotional exhaustion, depersonalization, and low personal accomplishment prevalence ranged from 0% to 86.2%, 0% to 89.9%, and 0% to 87.1%, respectively. Because of inconsistencies in definitions of and assessment methods for burnout across studies, associations between burnout and sex, age, geography, time, specialty, and depressive symptoms could not be reliably determined.
Conclusions and Relevance In this systematic review, there was substantial variability in prevalence estimates of burnout among practicing physicians and marked variation in burnout definitions, assessment methods, and study quality. These findings preclude definitive conclusions about the prevalence of burnout and highlight the importance of developing a consensus definition of burnout and of standardizing measurement tools to assess the effects of chronic occupational stress on physicians.

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The Lancet (15 September 2018, Vol. 392, No. 10151)

High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: A stepped-wedge, cluster-randomised controlled trial
Anoop S V Shah, Atul Anand, Fiona E Strachan, et al.
The Lancet: Volume 392, ISSUE 10151, P919-928, September 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31923-8/fulltext

Summary
Background
High-sensitivity cardiac troponin assays permit use of lower thresholds for the diagnosis of myocardial infarction, but whether this improves clinical outcomes is unknown. We aimed to determine whether the introduction of a high-sensitivity cardiac troponin I (hs-cTnI) assay with a sex-specific 99th centile diagnostic threshold would reduce subsequent myocardial infarction or cardiovascular death in patients with suspected acute coronary syndrome.
Methods
In this stepped-wedge, cluster-randomised controlled trial across ten secondary or tertiary care hospitals in Scotland, we evaluated the implementation of an hs-cTnI assay in consecutive patients who had been admitted to the hospitals' emergency departments with suspected acute coronary syndrome. Patients were eligible for inclusion if they presented with suspected acute coronary syndrome and had paired cardiac troponin measurements from the standard care and trial assays. During a validation phase of 6–12 months, results from the hs-cTnI assay were concealed from the attending clinician, and a contemporary cardiac troponin I (cTnI) assay was used to guide care. Hospitals were randomly allocated to early (n=5 hospitals) or late (n=5 hospitals) implementation, in which the high-sensitivity assay and sex-specific 99th centile diagnostic threshold was introduced immediately after

the 6-month validation phase or was deferred for a further 6 months. Patients reclassified by the high-sensitivity assay were defined as those with an increased hs-cTnI concentration in whom cTnI concentrations were below the diagnostic threshold on the contemporary assay. The primary outcome was subsequent myocardial infarction or death from cardiovascular causes at 1 year after initial presentation. Outcomes were compared in patients reclassified by the high-sensitivity assay before and after its implementation by use of an adjusted generalised linear mixed model. This trial is registered with ClinicalTrials.gov, number NCT01852123.

Findings

Between June 10, 2013, and March 3, 2016, we enrolled 48 282 consecutive patients (61 [SD 17] years, 47% women) of whom 10 360 (21%) patients had cTnI concentrations greater than those of the 99th centile of the normal range of values, who were identified by the contemporary assay or the high-sensitivity assay. The high-sensitivity assay reclassified 1771 (17%) of 10 360 patients with myocardial injury or infarction who were not identified by the contemporary assay. In those reclassified, subsequent myocardial infarction or cardiovascular death within 1 year occurred in 105 (15%) of 720 patients in the validation phase and 131 (12%) of 1051 patients in the implementation phase (adjusted odds ratio for implementation *vs* validation phase 1·10, 95% CI 0·75 to 1·61; p=0·620).

Interpretation

Use of a high-sensitivity assay prompted reclassification of 1771 (17%) of 10 360 patients with myocardial injury or infarction, but was not associated with a lower subsequent incidence of myocardial infarction or cardiovascular death at 1 year. Our findings question whether the diagnostic threshold for myocardial infarction should be based on the 99th centile derived from a normal reference population.

Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): A post-hoc analysis of prospective outcome data

Evangelos K Oikonomou, Mohamed Marwan, Milind Y Desai, et al.

The Lancet: Volume 392, ISSUE 10151, P929-939, September 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31114-0/fulltext

Summary

Background

Coronary artery inflammation inhibits adipogenesis in adjacent perivascular fat. A novel imaging biomarker—the perivascular fat attenuation index (FAI)—captures coronary inflammation by mapping spatial changes of perivascular fat attenuation on coronary computed tomography angiography (CTA). However, the ability of the perivascular FAI to predict clinical outcomes is unknown.

Methods

In the Cardiovascular RISk Prediction using Computed Tomography (CRISP-CT) study, we did a post-hoc analysis of outcome data gathered prospectively from two independent cohorts of consecutive patients undergoing coronary CTA in Erlangen, Germany (derivation cohort) and Cleveland, OH, USA (validation cohort). Perivascular fat attenuation mapping was done around the three major coronary arteries—the proximal right coronary artery, the left anterior descending artery, and the left circumflex artery. We assessed the prognostic value of perivascular fat attenuation mapping for all-cause and cardiac mortality in Cox regression models, adjusted for age, sex, cardiovascular risk

factors, tube voltage, modified Duke coronary artery disease index, and number of coronary CTA-derived high-risk plaque features.

Findings

Between 2005 and 2009, 1872 participants in the derivation cohort underwent coronary CTA (median age 62 years [range 17–89]). Between 2008 and 2016, 2040 patients in the validation cohort had coronary CTA (median age 53 years [range 19–87]). Median follow-up was 72 months (range 51–109) in the derivation cohort and 54 months (range 4–105) in the validation cohort. In both cohorts, high perivascular FAI values around the proximal right coronary artery and left anterior descending artery (but not around the left circumflex artery) were predictive of all-cause and cardiac mortality and correlated strongly with each other. Therefore, the perivascular FAI measured around the right coronary artery was used as a representative biomarker of global coronary inflammation (for prediction of cardiac mortality, hazard ratio [HR] 2·15, 95% CI 1·33–3·48; p=0·0017 in the derivation cohort, and 2·06, 1·50–2·83; p<0·0001 in the validation cohort). The optimum cutoff for the perivascular FAI, above which there is a steep increase in cardiac mortality, was ascertained as −70·1 Hounsfield units (HU) or higher in the derivation cohort (HR 9·04, 95% CI 3·35–24·40; p<0·0001 for cardiac mortality; 2·55, 1·65–3·92; p<0·0001 for all-cause mortality). This cutoff was confirmed in the validation cohort (HR 5·62, 95% CI 2·90–10·88; p<0·0001 for cardiac mortality; 3·69, 2·26–6·02; p<0·0001 for all-cause mortality). Perivascular FAI improved risk discrimination in both cohorts, leading to significant reclassification for all-cause and cardiac mortality.

Interpretation

The perivascular FAI enhances cardiac risk prediction and restratification over and above current state-of-the-art assessment in coronary CTA by providing a quantitative measure of coronary inflammation. High perivascular FAI values (cutoff ≥–70·1 HU) are an indicator of increased cardiac mortality and, therefore, could guide early targeted primary prevention and intensive secondary prevention in patients.

Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

Pascal Vranckx, Marco Valgimigli, Peter Jüni, et al.

The Lancet: Volume 392, ISSUE 10151, P940-949, September 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31858-0/fulltext

Summary

Background

We hypothesised that ticagrelor, in combination with aspirin for 1 month, followed by ticagrelor alone, improves outcomes after percutaneous coronary intervention compared with standard antiplatelet regimens.

Methods

GLOBAL LEADERS was a randomised, open-label superiority trial at 130 sites in 18 countries. Patients undergoing percutaneous coronary intervention with a biolimus A9-eluting stent for stable coronary artery disease or acute coronary syndromes were randomly assigned (1:1) to 75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy, or standard dual antiplatelet therapy with 75–100 mg aspirin daily plus either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months.

Randomisation was concealed, stratified by centre and clinical presentation (stable coronary artery disease *vs* acute coronary syndrome), and blocked, with randomly varied block sizes of two and four. The primary endpoint at 2 years was a composite of all-cause mortality or non-fatal centrally adjudicated new Q-wave myocardial infarction as assessed by a core lab in a blinded manner. The key secondary safety endpoint was site-reported bleeding assessed according to the Bleeding Academic Research Consortium criteria (grade 3 or 5). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01813435, and is closed to new participants, with follow-up completed.

Findings

Between July 1, 2013, and Nov 9, 2015, 15 968 participants were randomly assigned, 7980 to the experimental group and 7988 to the control group. At 2 years, 304 (3·81%) participants in the experimental group had died or had a non-fatal centrally adjudicated new Q-wave myocardial infarction, compared with 349 (4·37%) participants in the control group (rate ratio 0·87 [95% CI 0·75–1·01]; p=0·073]). There was no evidence for a difference in treatment effects for the primary endpoint across prespecified subgroups of acute coronary syndromes and stable coronary artery disease (p=0·93). Grade 3 or 5 bleeding occurred in 163 participants in the experimental group and 169 in the control group (2·04% *vs* 2·12%; rate ratio 0·97 [95% CI 0·78–1·20]; p=0·77).

Interpretation

Ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after percutaneous coronary intervention.

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The New England Journal of Medicine (13 September 2018, Vol. 379, No. 11)

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, Jeffrey H. Schwartz, Balarama Gundapaneni, et al. for the ATTR-ACT Study Investigators

N Engl J Med 2018; 379:1007-1016 September 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1805689

Abstract

Background

Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.

Methods

In a multicenter, international, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 441 patients with transthyretin amyloid cardiomyopathy in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. In the primary analysis, we hierarchically assessed all-cause mortality, followed by frequency of cardiovascular-related hospitalizations according to the Finkelstein–Schoenfeld method. Key secondary end points were the change from baseline to month 30 for the 6-minute walk test and the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS), in which higher scores indicate better health status.

Results

In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 per year vs. 0.70 per year; 95% CI, 0.56 to 0.81). At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-minute walk test (P<0.001) and a lower rate of decline in KCCQ-OS score (P<0.001). The incidence and types of adverse events were similar in the two groups.

Conclusions

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo.

Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis

Tanuja Chitnis, Douglas L. Arnold, Brenda Banwell, et al. for the PARADIGMS Study Group

N Engl J Med 2018; 379:1017-1027 September 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1800149

Abstract

Background

Treatment of patients younger than 18 years of age with multiple sclerosis has not been adequately examined in randomized trials. We compared fingolimod with interferon beta-1a in this population.

Methods

In this phase 3 trial, we randomly assigned patients 10 to 17 years of age with relapsing multiple sclerosis in a 1:1 ratio to receive oral fingolimod at a dose of 0.5 mg per day (0.25 mg per day for patients with a body weight of ≤40 kg) or intramuscular interferon beta-1a at a dose of 30 µg per week for up to 2 years. The primary end point was the annualized relapse rate.

Results

Of a total of 215 patients, 107 were assigned to fingolimod and 108 to interferon beta-1a. The mean age of the patients was 15.3 years. Among all patients, there was a mean of 2.4 relapses during the preceding 2 years. The adjusted annualized relapse rate was 0.12 with fingolimod and 0.67 with interferon beta-1a (absolute difference, 0.55 relapses; relative difference, 82%; P<0.001). The key secondary end point of the annualized rate of new or newly enlarged lesions on T2-weighted magnetic resonance imaging (MRI) was 4.39 with fingolimod and 9.27 with interferon beta-1a (absolute difference, 4.88 lesions; relative difference, 53%; P<0.001). Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a. Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in 4 patients) and leukopenia (in 2 patients). Six patients had convulsions. Serious adverse events occurred in 7 patients (6.5%) in the interferon beta-1a group and included infection (in 2 patients) and supraventricular tachycardia (in 1 patient).

Conclusions

Among pediatric patients with relapsing multiple sclerosis, fingolimod was associated with a lower rate of relapse and less accumulation of lesions on MRI over a 2-year period than

interferon beta-1a but was associated with a higher rate of serious adverse events. Longer studies are required to determine the durability and safety of fingolimod in pediatric multiple sclerosis.

Mutation Clearance after Transplantation for Myelodysplastic Syndrome

Eric J. Duncavage, Meagan A. Jacoby, Gue Su Chang, et al.

N Engl J Med 2018; 379:1028-1041 September 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1804714

Abstract

Background

Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for patients with myelodysplastic syndrome (MDS). The molecular predictors of disease progression after transplantation are unclear.

Methods

We sequenced bone marrow and skin samples from 90 adults with MDS who underwent allogeneic hematopoietic stem-cell transplantation after a myeloablative or reduced-intensity conditioning regimen. We detected mutations before transplantation using enhanced exome sequencing, and we evaluated mutation clearance by using error-corrected sequencing to genotype mutations in bone marrow samples obtained 30 days after transplantation. In this exploratory study, we evaluated the association of a mutation detected after transplantation with disease progression and survival.

Results

Sequencing identified at least one validated somatic mutation before transplantation in 86 of 90 patients (96%); 32 of these patients (37%) had at least one mutation with a maximum variant allele frequency of at least 0.5% (equivalent to 1 heterozygous mutant cell in 100 cells) 30 days after transplantation. Patients with disease progression had mutations with a higher maximum variant allele frequency at 30 days than those who did not (median maximum variant allele frequency, 0.9% vs. 0%; P<0.001). The presence of at least one mutation with a variant allele frequency of at least 0.5% at day 30 was associated with a higher risk of progression (53.1% vs. 13.0%; conditioning regimen–adjusted hazard ratio, 3.86; 95% confidence interval [CI], 1.96 to 7.62; P<0.001) and a lower 1-year rate of progression-free survival than the absence of such a mutation (31.3% vs. 59.3%; conditioning regimen–adjusted hazard ratio for progression or death, 2.22; 95% CI, 1.32 to 3.73; P=0.005). The rate of progression-free survival was lower among patients who had received a reduced-intensity conditioning regimen and had at least one persistent mutation with a variant allele frequency of at least 0.5% at day 30 than among patients with other combinations of conditioning regimen and mutation status (P≤0.001). Multivariate analysis confirmed that patients who had a mutation with a variant allele frequency of at least 0.5% detected at day 30 had a higher risk of progression (hazard ratio, 4.48; 95% CI, 2.21 to 9.08; P<0.001) and a lower 1-year rate of progression-free survival than those who did not (hazard ratio for progression or death, 2.39; 95% CI, 1.40 to 4.09; P=0.002).

Conclusions

The risk of disease progression was higher among patients with MDS in whom persistent disease–associated mutations were detected in the bone marrow 30 days after transplantation than among those in whom these mutations were not detected.

Brief Report

Essential Role of BRCA2 in Ovarian Development and Function
Ariella Weinberg-Shukron, Mariana Rachmiel, Paul Renbaum, et al.
N Engl J Med 2018; 379:1042-1049 September 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1800024

Summary
The causes of ovarian dysgenesis remain incompletely understood. Two sisters with XX ovarian dysgenesis carried compound heterozygous truncating mutations in the *BRCA2* gene that led to reduced BRCA2 protein levels and an impaired response to DNA damage, which resulted in chromosomal breakage and the failure of RAD51 to be recruited to double-stranded DNA breaks. The sisters also had microcephaly, and one sister was in long-term remission from leukemia, which had been diagnosed when she was 5 years old. Drosophila mutants that were null for an orthologue of *BRCA2* were sterile, and gonadal dysgenesis was present in both sexes. These results revealed a new role for *BRCA2* and highlight the importance to ovarian development of genes that are critical for recombination during meiosis.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
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The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access.	https://openathens.nice.org.uk/

Library News

ClinicalKey

ClinicalKey

ClinicalKey is a **clinical** search engine that makes it easier for clinicians and other healthcare professionals to find and apply relevant knowledge to help them make better decisions – anywhere, anytime, in any patient scenario.

Includes full-text journals, book chapters, images, graphs, monographs, videos and much more. Many available for download.

Access it via our website: http://www.derbyhospitalslibrary.co.uk/e-resources

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KnowledgeShare

Having trouble keeping up to date?

KnowledgeShare is a web-based current awareness system that provides a personalised current awareness service, direct to your inbox.

How it works: Let us know your areas of interest (e.g. physical conditions, professional interests such as mentoring, providing education) and we will set you up with an account. You will then receive regular emails targeted to your interests.

OpenAthens: You will need to have an NHS OpenAthens account registered with us, prior to setting up a **KnowledgeShare** account. To register for an Athens account, please go to: https://openathens.nice.org.uk

Further information can be found via this link:
http://www.derbyhospitalslibrary.co.uk/current-awareness

BMJ Case Reports

The Library and Knowledge Service now has full-text access to *BMJ Case Reports*. *"Case Reports is a unique & growing repository for all healthcare professionals & researchers to submit, search & view case reports in all disciplines."*

BMJ Case Reports can be access here: http://casereports.bmj.com. Click on Login via OpenAthens on the right hand side to log in.

Guidance for authors can be found at:
http://casereports.bmj.com/site/about/guidelines.xhtml

If you wish to submit a case report, the institutional fellowship code is 4315973. An additional fee needs to be paid by the author if s/he wishes to make their submission open access. Details can be found within the guidance.

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