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BMJ (1 September 2018, Vol. 362, No. 8165)

Assessment of the genetic and clinical determinants of fracture risk: Genome wide association and mendelian randomisation study

Katerina Trajanoska, John A Morris, Ling Oei, Hou-Feng Zheng, on behalf of the GEFOS/GENOMOS consortium and the 23andMe research team

BMJ 2018; 362 (Published 29 August 2018)
https://www.bmj.com/content/362/bmj.k3225

Abstract

Objectives To identify the genetic determinants of fracture risk and assess the role of 15 clinical risk factors on osteoporotic fracture risk.

Design Meta-analysis of genome wide association studies (GWAS) and a two-sample mendelian randomisation approach.

Setting 25 cohorts from Europe, United States, east Asia, and Australia with genome wide genotyping and fracture data.

Participants A discovery set of 37 857 fracture cases and 227 116 controls; with replication in up to 147 200 fracture cases and 150 085 controls. Fracture cases were defined as individuals (>18 years old) who had fractures at any skeletal site confirmed by medical, radiological, or questionnaire reports. Instrumental variable analyses were performed to estimate effects of 15 selected clinical risk factors for fracture in a two-sample mendelian randomisation framework, using the largest previously published GWAS meta-analysis of each risk factor.

Results Of 15 fracture associated loci identified, all were also associated with bone mineral density and mapped to genes clustering in pathways known to be critical to bone biology (e.g. *SOST*, *WNT16*, and *ESR1*) or novel pathways (*FAM210A*, *GRB10*, and *ETS2*). Mendelian randomisation analyses showed a clear effect of bone mineral density on fracture risk. One standard deviation decrease in genetically determined bone mineral density of the femoral neck was associated with a 55% increase in fracture risk (odds ratio 1.55 (95% confidence interval 1.48 to 1.63; $P=1.5\times10^{-68}$). Hand grip strength was inversely associated with fracture risk, but this result was not significant after multiple testing correction. The remaining clinical risk factors (including vitamin D levels) showed no evidence for an effect on fracture.

Conclusions This large scale GWAS meta-analysis for fracture identified 15 genetic determinants of fracture, all of which also influenced bone mineral density. Among the clinical risk factors for fracture assessed, only bone mineral density showed a major causal effect on fracture. Genetic predisposition to lower levels of vitamin D and estimated calcium intake from dairy sources were not associated with fracture risk.

Environmental toxic metal contaminants and risk of cardiovascular disease: Systematic review and meta-analysis

Rajiv Chowdhury, Anna Ramond, Linda M O'Keeffe, et al.

BMJ 2018; 362 (Published 29 August 2018)
https://www.bmj.com/content/362/bmj.k3310

Abstract

Objective To conduct a systematic review and meta-analysis of epidemiological studies investigating the association of arsenic, lead, cadmium, mercury, and copper with cardiovascular disease.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, and Web of Science searched up to December 2017.

Review methods Studies reporting risk estimates for total cardiovascular disease, coronary heart disease, and stroke for levels of arsenic, lead, cadmium, mercury, or copper were included. Two investigators independently extracted information on study characteristics and outcomes in accordance with PRISMA and MOOSE guidelines. Relative risks were standardised to a common scale and pooled across studies for each marker using random effects meta-analyses.

Results The review identified 37 unique studies comprising 348 259 non-overlapping participants, with 13 033 coronary heart disease, 4205 stroke, and 15 274 cardiovascular disease outcomes in aggregate. Comparing top versus bottom thirds of baseline levels, pooled relative risks for arsenic and lead were 1.30 (95% confidence interval 1.04 to 1.63) and 1.43 (1.16 to 1.76) for cardiovascular disease, 1.23 (1.04 to 1.45) and 1.85 (1.27 to 2.69) for coronary heart disease, and 1.15 (0.92 to 1.43) and 1.63 (1.14 to 2.34) for stroke. Relative risks for cadmium and copper were 1.33 (1.09 to 1.64) and 1.81 (1.05 to 3.11) for cardiovascular disease, 1.29 (0.98 to 1.71) and 2.22 (1.31 to 3.74) for coronary heart disease, and 1.72 (1.29 to 2.28) and 1.29 (0.77 to 2.17) for stroke. Mercury had no distinctive association with cardiovascular outcomes. There was a linear dose-response relation for arsenic, lead, and cadmium with cardiovascular disease outcomes.

Conclusion Exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular disease and coronary heart disease. Mercury is not associated with cardiovascular risk. These findings reinforce the importance of environmental toxic metals in cardiovascular risk, beyond the roles of conventional behavioural risk factors.

Contributions of prescribed and non-prescribed opioids to opioid related deaths: Population based cohort study in Ontario, Canada

Tara Gomes, Wayne Khuu, Diana Martins, et al.

BMJ 2018; 362 (Published 29 August 2018)
https://www.bmj.com/content/362/bmj.k3207

Abstract

Objective To describe the contributions of prescribed and non-prescribed opioids to opioid related deaths.
Design Population based cohort study.
Setting Ontario, Canada, from 1 January 2013 to 31 December 2016.
Participants All Ontarians who died of an opioid related cause.
Exposure Active opioid prescriptions, defined as those with a duration overlapping the date of death, and recent opioid prescriptions, defined as those dispensed in the 30 and 180 days preceding death. Postmortem toxicology results from the Drug and Drug/Alcohol Related Death database were used to characterise deaths on the basis of presence of prescribed and non-prescribed (that is, diverted or illicit) opioids, overall and stratified by year and age.
Results 2833 opioid related deaths occurred. An active opioid prescription on the date of death was relatively common but declined slightly throughout the study period (38.2% (241/631) in 2013 and 32.5% (278/855) in 2016; P for trend=0.03). Older people and women were relatively more likely to have an active opioid prescription at time of death. In 2016, 46% (169/364) of people aged 45-64 had an active opioid prescription compared with only 12% (8/69) among those aged 24 or younger (P for trend<0.001). Similarly, 46% (124/272) of women had an active opioid prescription at time of death compared with 26.4% (154/583) of men (P<0.001). Among people with active opioid prescriptions at time of death, 37.8% (375/993) also had evidence of a non-prescribed opioid on postmortem toxicology. By 2016, the non-prescribed opioid most commonly identified after death was fentanyl (41%; 47 of 115 cases). Among people without an active opioid prescription at time of death, fentanyl was detected in 20% (78/390) of deaths in 2013, increasing to 47.5% (274/577) by 2016 (P<0.001).
Conclusions Prescribed, diverted, and illicit opioids all play an important role in opioid related deaths. Although more than half of all opioid related deaths still involved prescription drugs (either dispensed or diverted) in 2016, the increased rate of deaths involving fentanyl between 2015 and 2016 is concerning and suggests the need for a multifactorial approach to this problem that considers both the prescribed and illicit opioid environments.

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JAMA: Journal of the American Medical Association (4 September 2018, Vol. 320, No. 9)

Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure: A Randomized Clinical Trial

Dorothy K. Hatsukami, Xianghua, Joni A. Jensen, et al

JAMA. 2018; 320 (9): 880-891.
https://jamanetwork.com/journals/jama/article-abstract/2698925

Abstract
Importance The optimal temporal approach for reducing nicotine to minimally or nonaddictive levels in all cigarettes sold in the United States has not been determined.
Objectives To determine the effects of immediate vs gradual reduction in nicotine content to very low levels and as compared with usual nicotine level cigarettes on biomarkers of toxicant exposure.
Design, Setting, and Participants A double-blind, randomized, parallel-design study with 2 weeks of baseline smoking and 20 weeks of intervention was conducted at 10 US sites.

A volunteer sample of daily smokers with no intention to quit within 30 days was recruited between July 2014 and September 2016, with the last follow-up completed in March 2017.
Interventions (1) Immediate reduction to 0.4 mg of nicotine per gram of tobacco cigarettes; (2) gradual reduction from 15.5 mg to 0.4 mg of nicotine per gram of tobacco cigarettes with 5 monthly dose changes; or (3) maintenance on 15.5 mg of nicotine per gram of tobacco cigarettes.
Main Outcomes and Measures Between-group differences in 3 co-primary biomarkers of smoke toxicant exposure: breath carbon monoxide (CO), urine 3-hydroxypropylmercapturic acid (3-HPMA, metabolite of acrolein), and urine phenanthrene tetraol (PheT, indicator of polycyclic aromatic hydrocarbons) calculated as area under the concentration-time curve over the 20 weeks of intervention.
Results Among 1250 randomized participants (mean age, 45 years; 549 women [44%]; 958 [77%] completed the trial), significantly lower levels of exposure were observed in the immediate vs gradual reduction group for CO (mean difference, −4.06 parts per million [ppm] [95% CI, −4.89 to −3.23]; $P < .0055$), 3-HPMA (ratio of geometric means, 0.83 [95% CI, 0.77 to 0.88]; $P < .0055$), and PheT (ratio of geometric means, 0.88 [95% CI, 0.83 to 0.93]; $P < .0055$). Significantly lower levels of exposure were observed in the immediate reduction vs control group for CO (mean difference, −3.38 [95% CI, −4.40 to −2.36]; $P < .0055$), 3-HPMA (ratio of geometric means, 0.81 [95% CI, 0.75 to 0.88]; $P < .0055$), and PheT (ratio of geometric means, 0.86 [95% CI, 0.81 to 0.92]; $P < .0055$). No significant differences were observed between the gradual reduction vs control groups for CO (mean difference, 0.68 [95% CI, −0.31 to 1.67]; $P = .18$), 3-HPMA (ratio of geometric means, 0.98 [95% CI, 0.91 to 1.06]; $P = .64$), and PheT (ratio of geometric means, 0.98 [95% CI, 0.92 to 1.04]; $P = .52$).
Conclusions and Relevance Among smokers, immediate reduction of nicotine in cigarettes led to significantly greater decreases in biomarkers of smoke exposure across time compared with gradual reduction or a control group, with no significant differences between gradual reduction and control.

Mandatory Medicare Bundled Payment Program for Lower Extremity Joint Replacement and Discharge to Institutional Postacute Care: Interim Analysis of the First Year of a 5-Year Randomized Trial

Amy Finkelstein, Yunan Ji, Neale Mahoney, et al

JAMA. 2018; 320 (9): 892-900. doi:10.1001/jama.2018.12346
https://jamanetwork.com/journals/jama/article-abstract/2698927

Abstract
Importance Bundled payments are an increasingly common alternative payment model for Medicare, yet there is limited evidence regarding their effectiveness.
Objective To report interim outcomes from the first year of implementation of a bundled payment model for lower extremity joint replacement (LEJR).
Design, Setting, and Participants As part of a 5-year, mandatory-participation randomized trial by the Centers for Medicare & Medicaid Services, eligible metropolitan statistical areas (MSAs) were randomized to the Comprehensive Care for Joint Replacement (CJR) bundled payment model for LEJR episodes or to a control group. In the first performance year, hospitals received bonus payments if Medicare spending for LEJR episodes was below the target price and hospitals met quality standards. This interim analysis reports first-year data on LEJR episodes starting April 1, 2016, with data collection through December 31, 2016.

Exposure Randomization of MSAs into the CJR bundled payment model group (75 assigned; 67 included) or to the control group without the CJR model (121 assigned; 121 included). Instrumental variable analysis was used to evaluate the relationship between inclusion of MSAs in the CJR model and outcomes.
Main Outcomes and Measures The primary outcome was share of LEJR admissions discharged to institutional postacute care. Secondary outcomes included the number of days in institutional postacute care, discharges to other locations, Medicare spending during the episode (overall and for institutional postacute care), net Medicare spending during the episode, LEJR patient volume and patient case mix, and quality-of-care measures.
Results Among the 196 MSAs and 1633 hospitals, 131 285 eligible LEJR procedures were performed during the study period (mean volume, 110 LEJR episodes per hospital) among 130 343 patients (mean age, 72.5 [SD, 0.91] years; 65% women; 90% white). The mean percentage of LEJR admissions discharged to institutional postacute care was 33.7% (SD, 11.2%) in the control group and was 2.9 percentage points lower (95% CI, −4.95 to −0.90 percentage points) in the CJR group. Mean Medicare spending for institutional postacute care per LEJR episode was $3871 (SD, $1394) in the control group and was $307 lower (95% CI, −$587 to −$27) in the CJR group. Mean overall Medicare spending per LEJR episode was $22 872 (SD, $3619) in the control group and was $453 lower (95% CI, −$909 to $3) in the CJR group, a statistically nonsignificant difference. None of the other secondary outcomes differed significantly between groups.
Conclusions and Relevance In this interim analysis of the first year of the CJR bundled payment model for LEJR among Medicare beneficiaries, MSAs covered by CJR, compared with those that were not, had a significantly lower percentage of discharges to institutional postacute care but no significant difference in total Medicare spending per LEJR episode. Further evaluation is needed as the program is more fully implemented.

Association of Hospital Participation in a Medicare Bundled Payment Program With Volume and Case Mix of Lower Extremity Joint Replacement Episodes
Amol S. Navathe, Joshua M. Liao, Sarah E. Dykstra, et al
JAMA. 2018; 320 (9): 901-910.
https://jamanetwork.com/journals/jama/article-abstract/2698926

Abstract
Importance Medicare's Bundled Payments for Care Improvement (BPCI) initiative for lower extremity joint replacement (LEJR) surgery has been associated with a reduction in episode spending and stable-to-improved quality. However, BPCI may create unintended effects by prompting participating hospitals to increase the overall volume of episodes paid for by Medicare, which could potentially eliminate program-related savings or prompt them to shift case mix to lower-risk patients.
Objective To evaluate whether hospital BPCI participation for LEJR was associated with changes in overall volume and case mix.
Design, Setting, and Participants Observational study using Medicare claims data and a difference-in-differences method to compare 131 markets (hospital referral regions) with at least 1 BPCI participant hospital (n = 322) and 175 markets with no participating hospitals (n = 1340), accounting for 580 043 Medicare beneficiaries treated before (January 2011-September 2013) and 462 161 after (October 2013-December 2015) establishing the BPCI initiative. Hospital-level case-mix changes were assessed by comparing 265 participating hospitals with a 1:1 propensity-matched set of nonparticipating hospitals from non-BPCI markets.

Exposures Hospital BPCI participation.
Main Outcomes and Measures Changes in market-level LEJR volume in the before vs after BPCI periods and changes in hospital-level case mix based on demographic, socioeconomic, clinical, and utilization factors.
Results Among the 1 717 243 Medicare beneficiaries who underwent LEJR (mean age, 75 years; 64% women; and 95% nonblack race/ethnicity), BPCI participation was not significantly associated with a change in overall market-level volume. The mean quarterly market volume in non-BPCI markets increased 3.8% from 3.8 episodes per 1000 beneficiaries before BPCI to 3.9 episodes per 1000 beneficiaries after BPCI was launched. For BPCI markets, the mean quarterly market volume increased 4.4% from 3.6 episodes per 1000 beneficiaries before BPCI to 3.8 episodes per 1000 beneficiaries after BPCI was launched. The adjusted difference-in-differences estimate between the market types was 0.32% (95% CI, −0.06% to 0.69%; $P = .10$). Among 20 demographic, socioeconomic, clinical, and utilization factors, BPCI participation was associated with differential changes in hospital-level case mix for only 1 factor, prior skilled nursing facility use (adjusted difference-in-differences estimate, −0.53%; 95% CI, −0.96% to −0.10%; $P = .01$) in BPCI vs non-BPCI markets.
Conclusions and Relevance In this observational study of Medicare beneficiaries who underwent LEJR, hospital participation in Bundled Payments for Care Improvement was not associated with changes in market-level lower extremity joint replacement volume and largely was not associated with changes in hospital case mix. These findings may provide reassurance regarding 2 potential unintended effects associated with bundled payments for LEJR.

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The Lancet (1 September 2018, Vol. 392, No. 10149)

Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial
Thomas Pilgrim, Raffaele Piccolo, Dik Heg, et al
The Lancet: Volume 392, ISSUE 10149, P737-746, September 01, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31715-X/fulltext

Summary
Background
Drug-eluting stents combining an ultrathin cobalt-chromium stent platform with a biodegradable polymer eluting sirolimus have been shown to be non-inferior or superior to thin-strut, durable-polymer, everolimus-eluting stents in terms of 1 year safety and efficacy outcomes.
Methods
In the randomised, single-blind, multicentre, non-inferiority BIOSCIENCE trial, we compared biodegradable-polymer sirolimus-eluting stents with durable-polymer everolimus-eluting stents in patients with chronic stable coronary artery disease or acute coronary syndromes. Here, we assess the final 5-year clinical outcomes of BIOSCIENCE with regards to the primary clinical outcome of target lesion failure, which was a composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularisation. The primary analysis was done by intention to treat. The BIOSCIENCE trial is registered with ClinicalTrials.gov, number NCT01443104.

Findings
2008 (95%) of 2119 patients recruited between March 1, 2012, and May 31, 2013, completed 5 years of follow-up. Target lesion failure occurred in 198 patients (cumulative incidence 20·2%) treated with biodegradable-polymer sirolimus-eluting stents and in 189 patients (18·8%) treated with durable-polymer everolimus-eluting stents (rate ratio [RR] 1·07, 95% CI 0·88–1·31; p=0·487). All-cause mortality was significantly higher in patients treated with biodegradable-polymer sirolimus-eluting stents than in those treated with durable-polymer everolimus-eluting stents (14·1% *vs* 10·3%; RR 1·36, 95% CI 1·06–1·75; p=0·017), driven by a difference in non-cardiovascular deaths. We observed no difference between groups in cumulative incidence of definite stent thrombosis at 5 years (1·6% in both groups; 1·02, 0·51–2·05; p=0·950).
Interpretation
5-year risk of target lesion failure among all-comer patients undergoing percutaneous coronary intervention is similar after implantation of ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents or thin-strut, durable-polymer, everolimus-eluting stents. Higher incidences of all-cause and non-cardiovascular mortality in patients treated with biodegradable-polymer stents eluting sirolimus than in those treated with durable-polymer stents eluting everolimus warrant careful observation in ongoing clinical trials.

A scalable, integrated intervention to engage people who inject drugs in HIV care and medication-assisted treatment (HPTN 074): A randomised, controlled phase 3 feasibility and efficacy study
William C Miller, Irving F Hoffman, Brett S Hanscom, et al
The Lancet: Volume 392, ISSUE 10149, P747-759, September 01, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31487-9/fulltext

Summary
Background
People who inject drugs (PWID) have a high incidence of HIV, little access to antiretroviral therapy (ART) and medication-assisted treatment (MAT), and high mortality. We aimed to assess the feasibility of a future controlled trial based on the incidence of HIV, enrolment, retention, and uptake of the intervention, and the efficacy of an integrated and flexible intervention on ART use, viral suppression, and MAT use.
Methods
This randomised, controlled vanguard study was run in Kyiv, Ukraine (one community site), Thai Nguyen, Vietnam (two district health centre sites), and Jakarta, Indonesia (one hospital site). PWID who were HIV infected (index participants) and non-infected injection partners were recruited as PWID network units and were eligible for screening if they were aged 18–45 years (updated to 18–60 years 8 months into study), and active injection drug users. Further eligibility criteria for index participants included a viral load of 1000 copies per mL or higher, willingness and ability to recruit at least one injection partner who would be willing to participate. Index participants were randomly assigned via a computer generated sequence accessed through a secure web portal (3:1) to standard of care or intervention, stratified by site. Masking of assignment was not possible due to the nature of intervention. The intervention comprised systems navigation, psychosocial counselling, and ART at any CD4 count. Local ART and MAT services were used. Participants were followed up for 12–24 months. The primary objective was to assess the feasibility of a future randomised controlled trial. To achieve this aim we looked at the following endpoints: HIV incidence among injection partners in the standard of care group, and enrolment and retention of HIV-infected PWID and their injection partners and the uptake

of the integrated intervention. The study was also designed to assess the feasibility, barriers, and uptake of the integrated intervention. Endpoints were assessed in a modified intention-to-treat population after exclusion of ineligible participants. This trial is registered on ClinicalTrials.gov, NCT02935296, and is active but not recruiting new participants.

Findings

Between Feb 5, 2015, and June 3, 2016, 3343 potential index participants were screened, of whom 502 (15%) were eligible and enrolled. 1171 injection partners were referred, and 806 (69%) were eligible and enrolled. Index participants were randomly assigned to intervention (126 [25%]) and standard of care (376 [75%]) groups. At week 52, most living index participants (389 [86%] of 451) and partners (567 [80%] of 710) were retained, and self-reported ART use was higher among index participants in the intervention group than those in the standard of care group (probability ratio [PR] 1·7, 95% CI 1·4–1·9). Viral suppression was also higher in the intervention group than in the standard of care group (PR 1·7, 95% CI 1·3–2·2). Index participants in the intervention group reported more MAT use at 52 weeks than those in the standard of care group (PR 1·7, 95% CI 1·3–2·2). Seven incident HIV infections occurred, and all in injection partners in the standard of care group (intervention incidence 0·0 per 100 person-years, 95% CI 0·0–1·7; standard of care incidence 1·0 per 100 person-years, 95% CI 0·4–2·1; incidence rate difference −1·0 per 100 person-years, 95% CI −2·1 to 1·1). No severe adverse events due to the intervention were recorded.

Interpretation

This vanguard study provides evidence that a flexible, scalable intervention increases ART and MAT use and reduces mortality among PWID. The low incidence of HIV in both groups impedes a future randomised, controlled trial, but given the strength of the effect of the intervention, its implementation among HIV-infected PWID should be considered.

Burden of disease in Brazil, 1990–2016: A systematic subnational analysis for the Global Burden of Disease Study 2016

GBD 2016 Brazil Collaborators

The Lancet: Volume 392, ISSUE 10149, P760-775, September 01, 2018

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31221-2/fulltext

Summary

Background

Political, economic, and epidemiological changes in Brazil have affected health and the health system. We used the Global Burden of Disease Study 2016 (GBD 2016) results to understand changing health patterns and inform policy responses.

Methods

We analysed GBD 2016 estimates for life expectancy at birth (LE), healthy life expectancy (HALE), all-cause and cause-specific mortality, years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life-years (DALYs), and risk factors for Brazil, its 26 states, and the Federal District from 1990 to 2016, and compared these with national estimates for ten comparator countries.

Findings

Nationally, LE increased from 68·4 years (95% uncertainty interval [UI] 68·0–68·9) in 1990 to 75·2 years (74·7–75·7) in 2016, and HALE increased from 59·8 years (57·1–62·1) to 65·5 years (62·5–68·0). All-cause age-standardised mortality rates decreased by 34·0% (33·4–34·5), while all-cause age-standardised DALY rates decreased by 30·2% (27·7–32·8); the magnitude of declines varied among states. In 2016, ischaemic heart disease was the leading cause of age-standardised YLLs, followed by interpersonal violence. Low

back and neck pain, sense organ diseases, and skin diseases were the main causes of YLDs in 1990 and 2016. Leading risk factors contributing to DALYs in 2016 were alcohol and drug use, high blood pressure, and high body-mass index.

Interpretation

Health improved from 1990 to 2016, but improvements and disease burden varied between states. An epidemiological transition towards non-communicable diseases and related risks occurred nationally, but later in some states, while interpersonal violence grew as a health concern. Policy makers can use these results to address health disparities.

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The New England Journal of Medicine (30 August 2018, Vol. 379, No. 9)

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

Johnny Mahlangu, Johannes Oldenburg, Ido Paz-Priel, et al.

N Engl J Med 2018; 379: 811-822 August 30, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1803550

Abstract

Background

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis. In a phase 3, multicenter trial, we investigated its use as prophylaxis in persons who have hemophilia A without factor VIII inhibitors.

Methods

We randomly assigned, in a 2:2:1 ratio, participants 12 years of age or older who had been receiving episodic treatment with factor VIII to receive a subcutaneous maintenance dose of emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C). The primary end point was the difference in rates of treated bleeding (group A vs. group C and group B vs. group C). Participants who had been receiving factor VIII prophylaxis received emicizumab at a maintenance dose of 1.5 mg per kilogram per week (group D); intraindividual comparisons were performed in those who had participated in a noninterventional study.

Results

A total of 152 participants were enrolled. The annualized bleeding rate was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, as compared with 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($P<0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, as compared with those in group C, who all had treated bleeding events. In the intraindividual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis ($P<0.001$). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors.

Conclusions

Emicizumab prophylaxis administered subcutaneously once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; more than half the participants who received prophylaxis had no treated

bleeding events. In an intraindividual comparison, emicizumab therapy led to a significantly lower bleeding rate than previous factor VIII prophylaxis.

Bacterial Factors That Predict Relapse after Tuberculosis Therapy

Roberto Colangeli, Hannah Jedrey, Soyeon Kim, et al. for the DMID 01-009/Tuberculosis Trials Consortium Study 22 Teams

N Engl J Med 2018; 379:823-833 August 30, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1715849

Abstract

Background

Approximately 5% of patients with drug-susceptible tuberculosis have a relapse after 6 months of first-line therapy, as do approximately 20% of patients after 4 months of short-course therapy. We postulated that by analyzing pretreatment isolates of Mycobacterium tuberculosis obtained from patients who subsequently had a relapse or were cured, we could determine any correlations between the minimum inhibitory concentration (MIC) of a drug below the standard resistance breakpoint and the relapse risk after treatment.

Methods

Using data from the Tuberculosis Trials Consortium Study 22 (development cohort), we assessed relapse and cure isolates to determine the MIC values of isoniazid and rifampin that were below the standard resistance breakpoint (0.1 μg per milliliter for isoniazid and 1.0 μg per milliliter for rifampin). We combined this analysis with clinical, radiologic, and laboratory data to generate predictive relapse models, which we validated by analyzing data from the DMID 01-009 study (validation cohort).

Results

In the development cohort, the mean (±SD) MIC of isoniazid below the breakpoint was 0.0334±0.0085 μg per milliliter in the relapse group and 0.0286±0.0092 μg per milliliter in the cure group, which represented a higher value in the relapse group by a factor of 1.17 (P=0.02). The corresponding MIC values of rifampin were 0.0695±0.0276 and 0.0453±0.0223 μg per milliliter, respectively, which represented a higher value in the relapse group by a factor of 1.53 (P<0.001). Higher MIC values remained associated with relapse in a multivariable analysis that included other significant between-group differences. In an analysis of receiver-operating-characteristic curves of relapse based on these MIC values, the area under the curve (AUC) was 0.779. In the development cohort, the AUC in a multivariable model that included MIC values was 0.875. In the validation cohort, the MIC values either alone or combined with other patient characteristics were also predictive of relapse, with AUC values of 0.964 and 0.929, respectively. The use of a model score for the MIC values of isoniazid and rifampin to achieve 75.0% sensitivity in cross-validation analysis predicted relapse with a specificity of 76.5% in the development cohort and a sensitivity of 70.0% and a specificity of 100% in the validation cohort.

Conclusions

In pretreatment isolates of M. tuberculosis with decrements of MIC values of isoniazid or rifampin below standard resistance breakpoints, higher MIC values were associated with a greater risk of relapse than lower MIC values.

Type 2 Poliovirus Detection after Global Withdrawal of Trivalent Oral Vaccine

Isobel M. Blake, Margarita Pons-Salort, Natalie A. Molodecky, et al.

N Engl J Med 2018; 379: 834-845 August 30, 2018

https://www.nejm.org/doi/full/10.1056/NEJMoa1716677

Abstract

Background

Mass campaigns with oral poliovirus vaccine (OPV) have brought the world close to the eradication of wild poliovirus. However, to complete eradication, OPV must itself be withdrawn to prevent outbreaks of vaccine-derived poliovirus (VDPV). Synchronized global withdrawal of OPV began with serotype 2 OPV (OPV2) in April 2016, which presented the first test of the feasibility of eradicating all polioviruses.

Methods

We analyzed global surveillance data on the detection of serotype 2 Sabin vaccine (Sabin-2) poliovirus and serotype 2 vaccine–derived poliovirus (VDPV2, defined as vaccine strains that are at least 0.6% divergent from Sabin-2 poliovirus in the viral protein 1 genomic region) in stool samples from 495,035 children with acute flaccid paralysis in 118 countries and in 8528 sewage samples from four countries at high risk for transmission; the samples were collected from January 1, 2013, through July 11, 2018. We used Bayesian spatiotemporal smoothing and logistic regression to identify and map risk factors for persistent detection of Sabin-2 poliovirus and VDPV2.

Results

The prevalence of Sabin-2 poliovirus in stool samples declined from 3.9% (95% confidence interval [CI], 3.5 to 4.3) at the time of OPV2 withdrawal to 0.2% (95% CI, 0.1 to 2.7) at 2 months after withdrawal, and the detection rate in sewage samples declined from 71.0% (95% CI, 61.0 to 80.0) to 13.0% (95% CI, 8.0 to 20.0) during the same period. However, 12 months after OPV2 withdrawal, Sabin-2 poliovirus continued to be detected in stool samples (<0.1%; 95% CI, <0.1 to 0.1) and sewage samples (8.0%; 95% CI, 5.0 to 13.0) because of the use of OPV2 in response to VDPV2 outbreaks. Nine outbreaks were reported after OPV2 withdrawal and were associated with low coverage of routine immunization (odds ratio, 1.64 [95% CI, 1.14 to 2.54] per 10% absolute decrease) and low levels of population immunity (odds ratio, 2.60 [95% CI, 1.35 to 5.59] per 10% absolute decrease) within affected countries.

Conclusions

High population immunity has facilitated the decline in the prevalence of Sabin-2 poliovirus after OPV2 withdrawal and restricted the circulation of VDPV2 to areas known to be at high risk for transmission. The prevention of VDPV2 outbreaks in these known areas before the accumulation of substantial cohorts of children susceptible to type 2 poliovirus remains a high priority.

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

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Abstract

Background

There are limited treatments for progressive multiple sclerosis. Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4 and can cross the blood–brain barrier, with potential salutary effects in progressive multiple sclerosis.

Methods

We enrolled patients with primary or secondary progressive multiple sclerosis in a phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks. The primary efficacy end point was the rate of brain atrophy, as measured by the brain parenchymal fraction (brain size relative to the volume of the outer surface contour of the brain). Major secondary end points included the change in the pyramidal tracts on diffusion tensor imaging, the magnetization transfer ratio in normal-appearing brain tissue, the thickness of the retinal nerve-fiber layer, and cortical atrophy, all measures of tissue damage in multiple sclerosis.

Results

Of 255 patients who underwent randomization, 129 were assigned to ibudilast and 126 to placebo. A total of 53% of the patients in the ibudilast group and 52% of those in the placebo group had primary progressive disease; the others had secondary progressive disease. The rate of change in the brain parenchymal fraction was −0.0010 per year with ibudilast and −0.0019 per year with placebo (difference, 0.0009; 95% confidence interval, 0.00004 to 0.0017; P=0.04), which represents approximately 2.5 ml less brain-tissue loss with ibudilast over a period of 96 weeks. Adverse events with ibudilast included gastrointestinal symptoms, headache, and depression.

Conclusions

In a phase 2 trial involving patients with progressive multiple sclerosis, ibudilast was associated with slower progression of brain atrophy than placebo but was associated with higher rates of gastrointestinal side effects, headache, and depression.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
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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/
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