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BMJ (17 March 2018, Vol. 360, No. 8145)

Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis

Shrujal Baxi, Annie Yang, Renee L Gennarelli, et al.

BMJ 2018; 360 :k793 (Published 14 March 2018)
http://www.bmj.com/content/360/bmj.k793

Abstract

Objective To evaluate rates of serious organ specific immune-related adverse events, general adverse events related to immune activation, and adverse events consistent with musculoskeletal problems for anti-programmed cell death 1 (PD-1) drugs overall and compared with control treatments.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, Cochrane Library, Web of Science, and Scopus searched to 16 March 2017 and combined with data from ClinicalTrials.gov.

Study selection Eligible studies included primary clinical trial data on patients with cancer with recurrent or metastatic disease.

Data extraction Three independent investigators extracted data on adverse events from ClinicalTrials.gov and the published studies. Risk of bias was assessed using the Cochrane tool by three independent investigators.

Results 13 relevant studies were included; adverse event data were available on ClinicalTrials.gov for eight. Studies compared nivolumab (n=6), pembrolizumab (5), or atezolizumab (2) with chemotherapy (11), targeted drugs (1), or both (1). Serious organ specific immune-related adverse events were rare, but compared with standard treatment, rates of hypothyroidism (odds ratio 7.56, 95% confidence interval 4.53 to 12.61), pneumonitis (5.37, 2.73 to 10.56), colitis (2.88, 1.30 to 6.37), and hypophysitis (3.38, 1.02 to 11.08) were increased with anti-PD-1 drugs. Of the general adverse events related to immune activation, only the rate of rash (2.34, 2.73 to 10.56) increased. Incidence of fatigue (32%) and diarrhea (19%) were high but similar to control. Reporting of adverse events consistent with musculoskeletal problems was inconsistent; rates varied but were over 20% in some studies for arthraligia and back pain.

Conclusions Organ specific immune-related adverse events are uncommon with anti-PD-1 drugs but the risk is increased compared with control treatments. General adverse events related to immune activation are largely similar. Adverse events consistent with musculoskeletal problems are inconsistently reported but adverse events may be common.

Relaxation of the one child policy and trends in caesarean section rates and birth outcomes in China between 2012 and 2016: observational study of nearly seven million health facility births

Juan Liang, Yi Mu, Xiaohong Li, et al.
BMJ 2018; 360 :k817 (Published 05 March 2018)
http://www.bmj.com/content/360/bmj.k817

Abstract

Objective To examine how the relaxation of the one child policy and policies to reduce caesarean section rates might have affected trends over time in caesarean section rates and perinatal and pregnancy related mortality in China.

Design Observational study.

Setting China's National Maternal Near Miss Surveillance System (NMNMSS).

Participants 6 838 582 births at 28 completed weeks or more of gestation or birth weight ≥1000 g in 438 hospitals in the NMNMSS between 2012 and 2016.

Main outcome measures Obstetric risk was defined using a modified Robson classification. The main outcome measures were changes in parity and age distributions and relative frequency of each Robson group, crude and adjusted trends over time in caesarean section rates within each risk category (using Poisson regression with a robust variance estimator), and trends in perinatal and pregnancy related mortality over time.

Results Caesarean section rates declined steadily between 2012 and 2016 (crude relative risk 0.91, 95% confidence interval 0.89 to 0.93), reaching an overall hospital based rate of 41.1% in 2016. The relaxation of the one child policy was associated with an increase in the proportion of multiparous births (from 34.1% in 2012 to 46.7% in 2016), and births in women with a uterine scar nearly doubled (from 9.8% to 17.7% of all births). Taking account of these changes, the decline in caesarean sections was amplified over time (adjusted relative risk 0.82, 95% confidence interval 0.81 to 0.84). Caesarean sections declined noticeably in nulliparous women (0.75, 0.73 to 0.77) but also declined in multiparous women without a uterine scar (0.65, 0.62 to 0.77). The decrease in caesarean section rates was most pronounced in hospitals with the highest rates in 2012, consistent with the government's policy of targeting hospitals with the highest rates. Perinatal mortality declined from 10.1 to 7.2 per 1000 births over the same period (0.87, 0.83 to 0.91), and there was no change in pregnancy related mortality over time.

Conclusions China is the only country that has succeeded in reverting the rising trends in caesarean sections. China's success is remarkable given that the changes in obstetric risk associated with the relaxation of the one child policy would have led to an increase in the need for caesarean sections. China's experience suggests that change is possible when strategies are comprehensive and deal with the system level factors that underpin overuse as well as the various incentives at work during a clinical encounter.

Impact of national cancer policies on cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study

Aimilia Exarchakou, Bernard Rachet, Aurélien Belot, et al.
BMJ 2018; 360 :k764 (Published 14 March 2018)
http://www.bmj.com/content/360/bmj.k764

Abstract

Objective To assess the effectiveness of the NHS Cancer Plan (2000) and subsequent national cancer policy initiatives in improving cancer survival and reducing socioeconomic inequalities in survival in England.

Design Population based cohort study.
Setting England.
Population More than 3.5 million registered patients aged 15-99 with a diagnosis of one of the 24 most common primary, malignant, invasive neoplasms between 1996 and 2013.
Main outcome measures Age standardised net survival estimates by cancer, sex, year, and deprivation group. These estimates were modelled using regression model with splines to explore changes in the cancer survival trends and in the socioeconomic inequalities in survival.
Results One year net survival improved steadily from 1996 for 26 of 41 sex-cancer combinations studied, and only from 2001 or 2006 for four cancers. Trends in survival accelerated after 2006 for five cancers. The deprivation gap observed for all 41 sex-cancer combinations among patients with a diagnosis in 1996 persisted until 2013. However, the gap slightly decreased for six cancers among men for which one year survival was more than 65% in 1996, and for cervical and uterine cancers, for which survival was more than 75% in 1996. The deprivation gap widened notably for brain tumours in men and for lung cancer in women.
Conclusions Little evidence was found of a direct impact of national cancer strategies on one year survival, and no evidence for a reduction in socioeconomic inequalities in cancer survival. These findings emphasise that socioeconomic inequalities in survival remain a major public health problem for a healthcare system founded on equity.

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JAMA: Journal of the American Medical Association (20 March 2018, Vol. 319, No. 11)

Effect of Offering Same-Day ART vs Usual Health Facility Referral During Home-Based HIV Testing on Linkage to Care and Viral Suppression among Adults with HIV in Lesotho: The CASCADE Randomized Clinical Trial

Niklaus D. Labhardt, Isaac Ringera, Thabo I. Lejone, et al.
JAMA. 2018;319(11):1103-1112. doi:10.1001/jama.2018.1818
https://jamanetwork.com/journals/jama/article-abstract/2674479

Abstract
Importance Home-based HIV testing is a frequently used strategy to increase awareness of HIV status in sub-Saharan Africa. However, with referral to health facilities, less than half of those who test HIV positive link to care and initiate antiretroviral therapy (ART).
Objective To determine whether offering same-day home-based ART to patients with HIV improves linkage to care and viral suppression in a rural, high-prevalence setting in sub-Saharan Africa.
Design, Setting, and Participants Open-label, 2-group, randomized clinical trial (February 22, 2016-September 17, 2017), involving 6 health care facilities in northern Lesotho. During home-based HIV testing in 6655 households from 60 rural villages and 17 urban areas, 278 individuals aged 18 years or older who tested HIV positive and were ART naive from 268 households consented and enrolled. Individuals from the same household were randomized into the same group.
Interventions Participants were randomly assigned to be offered same-day home-based ART initiation (n = 138) and subsequent follow-up intervals of 1.5, 3, 6, 9, and 12 months after treatment initiation at the health facility or to receive usual care (n = 140) with referral to the nearest health facility for preparatory counseling followed by ART initiation and monthly follow-up visits thereafter.

Main Outcomes and Measures Primary end points were rates of linkage to care within 3 months (presenting at the health facility within 90 days after the home visit) and viral suppression at 12 months, defined as a viral load of less than 100 copies/mL from 11 through 14 months after enrollment.
Results Among 278 randomized individuals (median age, 39 years [interquartile range, 28.0-52.0]; 180 women [65.7%]), 274 (98.6%) were included in the analysis (137 in the same-day group and 137 in the usual care group). In the same-day group, 134 (97.8%) indicated readiness to start ART that day and 2 (1.5%) within the next few days and were given a 1-month supply of ART. At 3 months, 68.6% (94) in same-day group vs 43.1% (59) in usual care group had linked to care (absolute difference, 25.6%; 95% CI, 13.8% to 36.3%; *P* < .001). At 12 months, 50.4% (69) in the same-day group vs 34.3% (47) in usual care group achieved viral suppression (absolute difference, 16.0%; 4.4%-27.2%; *P* = .007). Two deaths (1.5%) were reported in the same-day group, none in usual care group.
Conclusions and Relevance Among adults in rural Lesotho, a setting of high HIV prevalence, offering same-day home-based ART initiation to individuals who tested positive during home-based HIV testing, compared with usual care and standard clinic referral, significantly increased linkage to care at 3 months and HIV viral suppression at 12 months. These findings support the practice of offering same-day ART initiation during home-based HIV testing.
Trial Registration clinicaltrials.gov Identifier: NCT02692027

Quality of Health Care for Children in Australia, 2012-2013
Jeffrey Braithwaite, Peter D. Hibbert, Adam Jaffe, et al.
JAMA. 2018;319(11):1113-1124. doi:10.1001/jama.2018.0162
https://jamanetwork.com/journals/jama/article-abstract/2675548

Abstract
Importance The quality of routine care for children is rarely assessed, and then usually in single settings or for single clinical conditions.
Objective To estimate the quality of health care for children in Australia in inpatient and ambulatory health care settings.
Design, Setting, and Participants Multistage stratified sample with medical record review to assess adherence with quality indicators extracted from clinical practice guidelines for 17 common, high-burden clinical conditions (noncommunicable [n = 5], mental health [n = 4], acute infection [n = 7], and injury [n = 1]), such as asthma, attention-deficit/hyperactivity disorder, tonsillitis, and head injury. For these 17 conditions, 479 quality indicators were identified, with the number varying by condition, ranging from 9 for eczema to 54 for head injury. Four hundred medical records were targeted for sampling for each of 15 conditions while 267 records were targeted for anxiety and 133 for depression. Within each selected medical record, all visits for the 17 targeted conditions were identified, and separate quality assessments made for each. Care was evaluated for 6689 children 15 years of age and younger who had 15 240 visits to emergency departments, for inpatient admissions, or to pediatricians and general practitioners in selected urban and rural locations in 3 Australian states. These visits generated 160 202 quality indicator assessments.
Exposures Quality indicators were identified through a systematic search of local and international guidelines. Individual indicators were extracted from guidelines and assessed using a 2-stage Delphi process.
Main Outcomes and Measures Quality of care for each clinical condition and overall.

Results Of 6689 children with surveyed medical records, 53.6% were aged 0 to 4 years and 55.5% were male. Adherence to quality of care indicators was estimated at 59.8% (95% CI, 57.5%-62.0%; n = 160 202) across the 17 conditions, ranging from a high of 88.8% (95% CI, 83.0%-93.1%; n = 2638) for autism to a low of 43.5% (95% CI, 36.8%-50.4%; n = 2354) for tonsillitis. The mean adherence by condition category was estimated as 60.5% (95% CI, 57.2%-63.8%; n = 41 265) for noncommunicable conditions (range, 52.8%-75.8%); 82.4% (95% CI, 79.0%-85.5%; n = 14 622) for mental health conditions (range, 71.5%-88.8%); 56.3% (95% CI, 53.2%-59.4%; n = 94 037) for acute infections (range, 43.5%-69.8%); and 78.3% (95% CI, 75.1%-81.2%; n = 10 278) for injury.
Conclusions and Relevance Among a sample of children receiving care in Australia in 2012-2013, the overall prevalence of adherence to quality of care indicators for important conditions was not high. For many of these conditions, the quality of care may be inadequate.

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The Lancet (17 March 2018, Vol. 391, No. 10125)

Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries

Claudia Allemani, Tomohiro Matsuda, Veronica Di Carlo, et al. for the CONCORD Working Group

The Lancet Volume 391, No. 10125, p1023–1075, 17 March 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)33326-3/fulltext

Summary
Background
In 2015, the second cycle of the CONCORD programme established global surveillance of cancer survival as a metric of the effectiveness of health systems and to inform global policy on cancer control. CONCORD-3 updates the worldwide surveillance of cancer survival to 2014.
Methods
CONCORD-3 includes individual records for 37·5 million patients diagnosed with cancer during the 15-year period 2000–14. Data were provided by 322 population-based cancer registries in 71 countries and territories, 47 of which provided data with 100% population coverage. The study includes 18 cancers or groups of cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate, and melanoma of the skin in adults, and brain tumours, leukaemias, and lymphomas in both adults and children. Standardised quality control procedures were applied; errors were rectified by the registry concerned. We estimated 5-year net survival. Estimates were age-standardised with the International Cancer Survival Standard weights.
Findings
For most cancers, 5-year net survival remains among the highest in the world in the USA and Canada, in Australia and New Zealand, and in Finland, Iceland, Norway, and Sweden. For many cancers, Denmark is closing the survival gap with the other Nordic countries. Survival trends are generally increasing, even for some of the more lethal cancers: in some countries, survival has increased by up to 5% for cancers of the liver, pancreas, and lung. For women diagnosed during 2010–14, 5-year survival for breast cancer is now

89·5% in Australia and 90·2% in the USA, but international differences remain very wide, with levels as low as 66·1% in India. For gastrointestinal cancers, the highest levels of 5-year survival are seen in southeast Asia: in South Korea for cancers of the stomach (68·9%), colon (71·8%), and rectum (71·1%); in Japan for oesophageal cancer (36·0%); and in Taiwan for liver cancer (27·9%). By contrast, in the same world region, survival is generally lower than elsewhere for melanoma of the skin (59·9% in South Korea, 52·1% in Taiwan, and 49·6% in China), and for both lymphoid malignancies (52·5%, 50·5%, and 38·3%) and myeloid malignancies (45·9%, 33·4%, and 24·8%). For children diagnosed during 2010–14, 5-year survival for acute lymphoblastic leukaemia ranged from 49·8% in Ecuador to 95·2% in Finland. 5-year survival from brain tumours in children is higher than for adults but the global range is very wide (from 28·9% in Brazil to nearly 80% in Sweden and Denmark).

Interpretation

The CONCORD programme enables timely comparisons of the overall effectiveness of health systems in providing care for 18 cancers that collectively represent 75% of all cancers diagnosed worldwide every year. It contributes to the evidence base for global policy on cancer control. Since 2017, the Organisation for Economic Co-operation and Development has used findings from the CONCORD programme as the official benchmark of cancer survival, among their indicators of the quality of health care in 48 countries worldwide. Governments must recognise population-based cancer registries as key policy tools that can be used to evaluate both the impact of cancer prevention strategies and the effectiveness of health systems for all patients diagnosed with cancer.

Funding

American Cancer Society; Centers for Disease Control and Prevention; Swiss Re; Swiss Cancer Research foundation; Swiss Cancer League; Institut National du Cancer; La Ligue Contre le Cancer; Rossy Family Foundation; US National Cancer Institute; and the Susan G Komen Foundation.

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, et al.

The Lancet Volume 391, No. 10125, p1076–1084, 17 March 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30206-X/fulltext

Summary

Background

Evidence is scarce on the relative risk-benefit of inhaled triple therapy, consisting of inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting β_2-agonist, versus dual bronchodilation for chronic obstructive pulmonary disease (COPD). We aimed to compare a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) versus a single-inhaler dual bronchodilator combination of indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

Methods

This randomised, parallel-group, double-blind, double-dummy study was done at 187 sites across 17 countries. Eligible patients had symptomatic COPD, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication. After a 2 week run-in period with one inhalation per day of IND/GLY (85 µg/43 µg), patients were randomly assigned (1:1), via

an interactive response technology system, to receive 52 weeks of treatment with two inhalations of extrafine BDP/FF/G (87 µg/5 µg/9 µg) twice per day or one inhalation of IND/GLY (85 µg/43 µg) per day. Randomisation was stratified by country and severity of airflow limitation. The primary endpoint was the rate of moderate-to-severe COPD exacerbations across 52 weeks of treatment in all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02579850.

Findings

Between May, 29 2015, and July 10, 2017, 1532 patients received BDP/FF/G (n=764) or IND/GLY (n=768). Moderate-to-severe exacerbation rates were 0·50 per patient per year (95% CI 0·45–0·57) for BDP/FF/G and 0·59 per patient per year (0·53–0·67) for IND/GLY, giving a rate ratio of 0·848 (0·723–0·995, p=0·043) in favour of BDP/FF/G. Adverse events were reported by 490 (64%) of 764 patients receiving BDP/FF/G and 516 (67%) of 768 patients receiving IND/GLY. Pneumonia occurred in 28 (4%) patients receiving BDP/FF/G versus 27 (4%) patients receiving IND/GLY. One treatment-related serious adverse event occurred in each group: dysuria in a patient receiving BDP/FF/G and atrial fibrillation in a patient receiving IND/GLY.

Interpretation

In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia.

Funding

Chiesi Farmaceutici.

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

Elizabeth A Thiele, Eric D Marsh, Jacqueline A French, et al. on behalf of the GWPCARE4 Study Group

The Lancet Volume 391, No. 10125, p1085–1096, 17 March 2018

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30136-3/fulltext

Summary

Background

Patients with Lennox-Gastaut syndrome, a rare, severe form of epileptic encephalopathy, are frequently treatment resistant to available medications. No controlled studies have investigated the use of cannabidiol for patients with seizures associated with Lennox-Gastaut syndrome. We therefore assessed the efficacy and safety of cannabidiol as an add-on anticonvulsant therapy in this population of patients.

Methods

In this randomised, double-blind, placebo-controlled trial done at 24 clinical sites in the USA, the Netherlands, and Poland, we investigated the efficacy of cannabidiol as add-on therapy for drop seizures in patients with treatment-resistant Lennox-Gastaut syndrome. Eligible patients (aged 2–55 years) had Lennox-Gastaut syndrome, including a history of slow (<3 Hz) spike-and-wave patterns on electroencephalogram, evidence of more than one type of generalised seizure for at least 6 months, at least two drop seizures per week during the 4-week baseline period, and had not responded to treatment with at least two antiepileptic drugs. Patients were randomly assigned (1:1) using an interactive voice response system, stratified by age group, to receive 20 mg/kg oral cannabidiol daily or

matched placebo for 14 weeks. All patients, caregivers, investigators, and individuals assessing data were masked to group assignment. The primary endpoint was percentage change from baseline in monthly frequency of drop seizures during the treatment period, analysed in all patients who received at least one dose of study drug and had post-baseline efficacy data. All randomly assigned patients were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02224690.

Findings

Between April 28, 2015, and Oct 15, 2015, we randomly assigned 171 patients to receive cannabidiol (n=86) or placebo (n=85). 14 patients in the cannabidiol group and one in the placebo group discontinued study treatment; all randomly assigned patients received at least one dose of study treatment and had post-baseline efficacy data. The median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannibidiol group and 21·8% (IQR −45·7 to 1·7) in the placebo group. The estimated median difference between the treatment groups was −17·21 (95% CI −30·32 to −4·09; p=0·0135) during the 14-week treatment period. Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and 59 (69%) of 85 patients in the placebo group; most were mild or moderate. The most common adverse events were diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. 12 (14%) patients in the cannabidiol group and one (1%) patient in the placebo group withdrew from the study because of adverse events. One patient (1%) died in the cannabidiol group, but this was considered unrelated to treatment.

Interpretation

Add-on cannabidiol is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated. The long-term efficacy and safety of cannabidiol is currently being assessed in the open-label extension of this trial.

Funding

GW Pharmaceuticals.

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The New England Journal of Medicine (15 March 2018, Vol. 378, No. 11)

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

Bruno Hoen, Bruno Schaub, Anna L. Funk, et al.

N Engl J Med 2018; 378:985-994. March 15, 2018. DOI: 10.1056/NEJMoa1709481
http://www.nejm.org/doi/full/10.1056/NEJMoa1709481

Abstract

Background

The risk of congenital neurologic defects related to Zika virus (ZIKV) infection has ranged from 6 to 42% in various reports. The aim of this study was to estimate this risk among pregnant women with symptomatic ZIKV infection in French territories in the Americas.

Methods

From March 2016 through November 2016, we enrolled in this prospective cohort study pregnant women with symptomatic ZIKV infection that was confirmed by polymerase-chain-reaction (PCR) assay. The analysis included all data collected up to April 27, 2017, the date of the last delivery in the cohort.

Results

Among the 555 fetuses and infants in the 546 pregnancies included in the analysis, 28 (5.0%) were not carried to term or were stillborn, and 527 were born alive. Neurologic and

ocular defects possibly associated with ZIKV infection were seen in 39 fetuses and infants (7.0%; 95% confidence interval, 5.0 to 9.5); of these, 10 were not carried to term because of termination of pregnancy for medical reasons, 1 was stillborn, and 28 were live-born. Microcephaly (defined as head circumference more than 2 SD below the mean for sex and gestational age) was detected in 32 fetuses and infants (5.8%), of whom 9 (1.6%) had severe microcephaly (more than 3 SD below the mean). Neurologic and ocular defects were more common when ZIKV infection occurred during the first trimester (24 of 189 fetuses and infants [12.7%]) than when it occurred during the second trimester (9 of 252 [3.6%]) or third trimester (6 of 114 [5.3%]) (P=0.001).

Conclusions

Among pregnant women with symptomatic, PCR-confirmed ZIKV infection, birth defects possibly associated with ZIKV infection were present in 7% of fetuses and infants. Defects occurred more frequently in fetuses and infants whose mothers had been infected early in pregnancy. Longer-term follow-up of infants is required to assess any manifestations not detected at birth. (Funded by the French Ministry of Health and others; ClinicalTrials.gov number, NCT02916732.)

Injection of Cultured Cells with a ROCK Inhibitor for Bullous Keratopathy

Shigeru Kinoshita, Noriko Koizumi, Morio Ueno, et al.
N Engl J Med 2018; 378:995-1003. March 15, 2018. DOI: 10.1056/NEJMoa1712770
http://www.nejm.org/doi/full/10.1056/NEJMoa1712770

Abstract

Background

Corneal endothelial cell (CEC) disorders, such as Fuchs's endothelial corneal dystrophy, induce abnormal corneal hydration and result in corneal haziness and vision loss known as bullous keratopathy. We investigated whether injection of cultured human CECs supplemented with a rho-associated protein kinase (ROCK) inhibitor into the anterior chamber could increase CEC density.

Methods

We performed an uncontrolled, single-group study involving 11 persons who had received a diagnosis of bullous keratopathy and had no detectable CECs. Human CECs were cultured from a donor cornea; a total of 1×106 passaged cells were supplemented with a ROCK inhibitor (final volume, 300 µl) and injected into the anterior chamber of the eye that was selected for treatment. After the procedure, patients were placed in a prone position for 3 hours. The primary outcome was restoration of corneal transparency, with a CEC density of more than 500 cells per square millimeter at the central cornea at 24 weeks after cell injection. Secondary outcomes were a corneal thickness of less than 630 µm and an improvement in best corrected visual acuity equivalent to two lines or more on a Landolt C eye chart at 24 weeks after cell injection.

Results

At 24 weeks after cell injection, we recorded a CEC density of more than 500 cells per square millimeter (range, 947 to 2833) in 11 of the 11 treated eyes (100%; 95% confidence interval [CI], 72 to 100), of which 10 had a CEC density exceeding 1000 cells per square millimeter. A corneal thickness of less than 630 µm (range, 489 to 640) was attained in 10 of the 11 treated eyes (91%; 95% CI, 59 to 100), and an improvement in best corrected visual acuity of two lines or more was recorded in 9 of the 11 treated eyes (82%; 95% CI, 48 to 98).

Conclusions

Injection of human CECs supplemented with a ROCK inhibitor was followed by an increase in CEC density after 24 weeks in 11 persons with bullous keratopathy. (Funded by the Japan Agency for Medical Research and Development and others; UMIN number, UMIN000012534.)

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

Síle F. Molloy, Cecilia Kanyama, Robert S. Heyderman, et al. for the ACTA Trail Study Team

N Engl J Med 2018; 378:1004-1017. March 15, 2018. DOI: 10.1056/NEJMoa1710922
http://www.nejm.org/doi/full/10.1056/NEJMoa1710922

Abstract

Background

Cryptococcal meningitis accounts for more than 100,000 human immunodeficiency virus (HIV)–related deaths per year. We tested two treatment strategies that could be more sustainable in Africa than the standard of 2 weeks of amphotericin B plus flucytosine and more effective than the widely used fluconazole monotherapy.

Methods

We randomly assigned HIV-infected adults with cryptococcal meningitis to receive an oral regimen (fluconazole [1200 mg per day] plus flucytosine [100 mg per kilogram of body weight per day] for 2 weeks), 1 week of amphotericin B (1 mg per kilogram per day), or 2 weeks of amphotericin B (1 mg per kilogram per day). Each patient assigned to receive amphotericin B was also randomly assigned to receive fluconazole or flucytosine as a partner drug. After induction treatment, all the patients received fluconazole consolidation therapy and were followed to 10 weeks.

Results

A total of 721 patients underwent randomization. Mortality in the oral-regimen, 1-week amphotericin B, and 2-week amphotericin B groups was 18.2% (41 of 225), 21.9% (49 of 224), and 21.4% (49 of 229), respectively, at 2 weeks and was 35.1% (79 of 225), 36.2% (81 of 224), and 39.7% (91 of 229), respectively, at 10 weeks. The upper limit of the one-sided 97.5% confidence interval for the difference in 2-week mortality was 4.2 percentage points for the oral-regimen group versus the 2-week amphotericin B groups and 8.1 percentage points for the 1-week amphotericin B groups versus the 2-week amphotericin B groups, both of which were below the predefined 10-percentage-point noninferiority margin. As a partner drug with amphotericin B, flucytosine was superior to fluconazole (71 deaths [31.1%] vs. 101 deaths [45.0%]; hazard ratio for death at 10 weeks, 0.62; 95% confidence interval [CI], 0.45 to 0.84; P=0.002). One week of amphotericin B plus flucytosine was associated with the lowest 10-week mortality (24.2%; 95% CI, 16.2 to 32.1). Side effects, such as severe anemia, were more frequent with 2 weeks than with 1 week of amphotericin B or with the oral regimen.

Conclusions

One week of amphotericin B plus flucytosine and 2 weeks of fluconazole plus flucytosine were effective as induction therapy for cryptococcal meningitis in resource-limited settings. (ACTA Current Controlled Trials number, ISRCTN45035509.)

Variant Intestinal-Cell Kinase in Juvenile Myoclonic Epilepsy

Julia N. Bailey, Laurence de Nijs, Dongsheng Bai, et al.

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http://www.nejm.org/doi/full/10.1056/NEJMoa1700175

Abstract

Background

In juvenile myoclonic epilepsy, data are limited on the genetic basis of networks promoting convulsions with diffuse polyspikes on electroencephalography (EEG) and the subtle microscopic brain dysplasia called microdysgenesis.

Methods

Using Sanger sequencing, we sequenced the exomes of six members of a large family affected with juvenile myoclonic epilepsy and confirmed cosegregation in all 37 family members. We screened an additional 310 patients with this disorder for variants on DNA melting-curve analysis and targeted real-time DNA sequencing of the gene encoding intestinal-cell kinase (ICK). We calculated Bayesian logarithm of the odds (LOD) scores for cosegregating variants, odds ratios in case–control associations, and allele frequencies in the Genome Aggregation Database. We performed functional tests of the effects of variants on mitosis, apoptosis, and radial neuroblast migration in vitro and conducted video-EEG studies in mice lacking a copy of Ick.

Results

A variant, K305T (c.914A→C), cosegregated with epilepsy or polyspikes on EEG in 12 members of the family affected with juvenile myoclonic epilepsy. We identified 21 pathogenic ICK variants in 22 of 310 additional patients (7%). Four strongly linked variants (K220E, K305T, A615T, and R632X) impaired mitosis, cell-cycle exit, and radial neuroblast migration while promoting apoptosis. Tonic–clonic convulsions and polyspikes on EEG resembling seizures in human juvenile myoclonic epilepsy occurred more often in knockout heterozygous mice than in wild-type mice (P=0.02) during light sleep with isoflurane anesthesia.

Conclusions

Our data provide evidence that heterozygous variants in ICK caused juvenile myoclonic epilepsy in 7% of the patients included in our analysis. Variant ICK affects cell processes that help explain microdysgenesis and polyspike networks observed on EEG in juvenile myoclonic epilepsy. (Funded by the National Institutes of Health and others.)

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
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/

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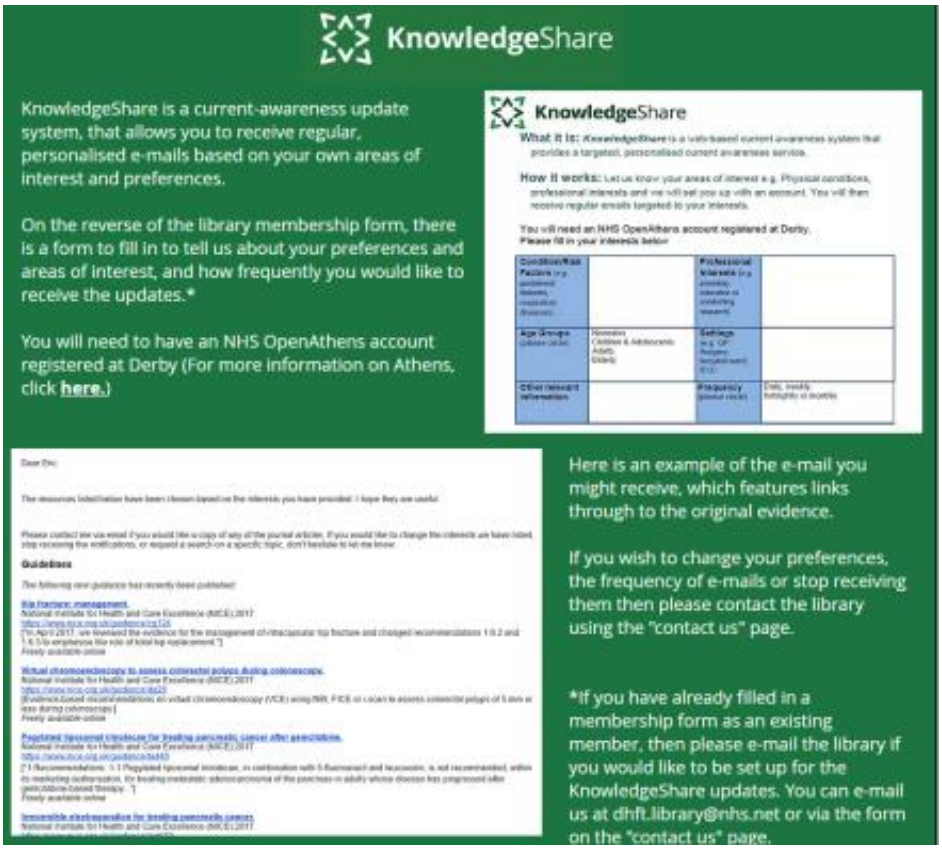

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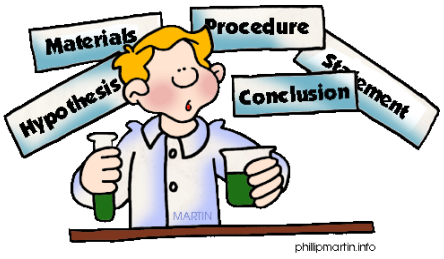

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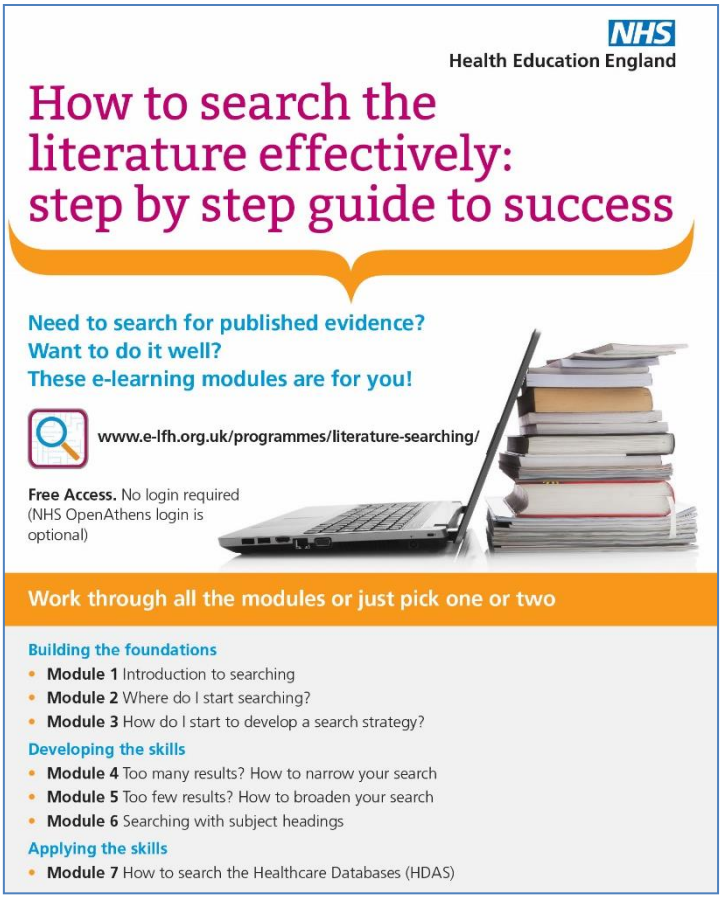

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