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BMJ (30 June 2018, Vol. 361, No. 8159)

Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: Population based matched cohort study
Kimberly G Blumenthal, Na Lu, Yuqing Zhang, et al.
BMJ 2018; 361 (Published 27 June 2018)
https://www.bmj.com/content/361/bmj.k2400

Abstract
Objective To evaluate the relation between penicillin allergy and development of meticillin resistant *Staphylococcus aureus* (MRSA) and *C difficile*.
Design Population based matched cohort study.
Setting United Kingdom general practice (1995-2015).
Participants 301 399 adults without previous MRSA or *C difficile* enrolled in the Health Improvement Network database: 64 141 had a penicillin allergy and 237 258 comparators matched on age, sex, and study entry time.
Main outcome measures The primary outcome was risk of incident MRSA and *C difficile*. Secondary outcomes were use of β lactam antibiotics and β lactam alternative antibiotics.
Results Among 64 141 adults with penicillin allergy and 237 258 matched comparators, 1365 developed MRSA (442 participants with penicillin allergy and 923 comparators) and 1688 developed *C difficile* (442 participants with penicillin allergy and 1246 comparators) during a mean 6.0 years of follow-up. Among patients with penicillin allergy the adjusted hazard ratio for MRSA was 1.69 (95% confidence interval 1.51 to 1.90) and for *C difficile* was 1.26 (1.12 to 1.40). The adjusted incidence rate ratios for antibiotic use among patients with penicillin allergy were 4.15 (95% confidence interval 4.12 to 4.17) for macrolides, 3.89 (3.66 to 4.12) for clindamycin, and 2.10 (2.08 to 2.13) for fluoroquinolones. Increased use of β lactam alternative antibiotics accounted for 55% of the increased risk of MRSA and 35% of the increased risk of *C difficile*.
Conclusions Documented penicillin allergy was associated with an increased risk of MRSA and *C difficile* that was mediated by the increased use of β lactam alternative antibiotics. Systematically addressing penicillin allergies may be an important public health

strategy to reduce the incidence of MRSA and *C difficile* among patients with a penicillin allergy label.

Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: Randomised, open label, non-inferiority trial

Dominik Abt, Lukas Hechelhammer, Gautier Müllhaupt, et al.
BMJ 2018; 361 (Published 19 June 2018)
https://www.bmj.com/content/361/bmj.k2338

Abstract

Objective To compare prostatic artery embolisation (PAE) with transurethral resection of the prostate (TURP) in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia in terms of patient reported and functional outcomes.

Design Randomised, open label, non-inferiority trial.

Setting Urology and radiology departments of a Swiss tertiary care centre.

Participants 103 patients aged ≥40 years with refractory lower urinary tract symptoms secondary to benign prostatic hyperplasia were randomised between 11 February 2014 and 24 May 2017; 48 and 51 patients reached the primary endpoint 12 weeks after PAE and TURP, respectively.

Interventions PAE performed with 250-400 µm microspheres under local anaesthesia versus monopolar TURP performed under spinal or general anaesthesia.

Main outcomes and measures Primary outcome was change in international prostate symptoms score (IPSS) from baseline to 12 weeks after surgery; a difference of less than 3 points between treatments was defined as non-inferiority for PAE and tested with a one sided *t* test. Secondary outcomes included further questionnaires, functional measures, magnetic resonance imaging findings, and adverse events; changes from baseline to 12 weeks were compared between treatments with two sided tests for superiority.

Results Mean reduction in IPSS from baseline to 12 weeks was −9.23 points after PAE and −10.77 points after TURP. Although the difference was less than 3 points (1.54 points in favour of TURP (95% confidence interval −1.45 to 4.52)), non-inferiority of PAE could not be shown (P=0.17). None of the patient reported secondary outcomes differed significantly between treatments when tested for superiority; IPSS also did not differ significantly (P=0.31). At 12 weeks, PAE was less effective than TURP regarding changes in maximum rate of urinary flow (5.19 *v* 15.34 mL/s; difference 10.15 (95% confidence interval −14.67 to −5.63); P<0.001), postvoid residual urine (−86.36 *v* −199.98 mL; 113.62 (39.25 to 187.98); P=0.003), prostate volume (−12.17 *v* −30.27 mL; 18.11 (10.11 to 26.10); P<0.001), and desobstructive effectiveness according to pressure flow studies (56% *v* 93% shift towards less obstructive category; P=0.003). Fewer adverse events occurred after PAE than after TURP (36 *v* 70 events; P=0.003).

Conclusions The improvement in lower urinary tract symptoms secondary to benign prostatic hyperplasia seen 12 weeks after PAE is close to that after TURP. PAE is associated with fewer complications than TURP but has disadvantages regarding functional outcomes, which should be considered when selecting patients. Further comparative study findings, including longer follow-up, should be evaluated before PAE can be considered as a routine treatment.

Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies: Exploratory case-control study
Joanne E Given, Maria Loane, Ester Garne, et al.
BMJ 2018; 361 (Published 25 June 2018)
https://www.bmj.com/content/361/bmj.k2477

Abstract
Objective To investigate whether exposure to metformin during the first trimester of pregnancy, for diabetes or other indications, increases the risk of all or specific congenital anomalies.
Design Population based exploratory case-control study using malformed controls. Cases of 29 specific subgroups of non-genetic anomalies, and all non-genetic anomalies combined, were compared with controls (all other non-genetic anomalies or genetic syndromes).
Setting 11 EUROmediCAT European congenital anomaly registries surveying 1 892 482 births in Europe between 2006 and 2013.
Participants 50 167 babies affected by congenital anomaly (41 242 non-genetic and 8925 genetic) including live births, fetal deaths from 20 weeks' gestation, and terminations of pregnancy for fetal anomaly.
Main outcome measure Odds ratios adjusted for maternal age, registry, multiple birth, and maternal diabetes status.
Results 168 babies affected by congenital anomaly (141 non-genetic and 27 genetic) were exposed to metformin, 3.3 per 1000 births. No evidence was found for a higher proportion of exposure to metformin during the first trimester among babies with all non-genetic anomalies combined compared with genetic controls (adjusted odds ratio 0.84, 95% confidence interval 0.55 to 1.30). The only significant result was for pulmonary valve atresia (adjusted odds ratio 3.54, 1.05 to 12.00, compared with non-genetic controls; 2.86, 0.79 to 10.30, compared with genetic controls).
Conclusions No evidence was found for an increased risk of all non-genetic congenital anomalies combined following exposure to metformin during the first trimester, and the one significant association was no more than would be expected by chance. Further surveillance is needed to increase sample size and follow up the cardiac signal, but these findings are reassuring given the increasing use of metformin in pregnancy.

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JAMA: Journal of the American Medical Association (3 July 2018, Vol. 320, No. 1)

Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial
Gina Suzanne Ogilvie, Dirk van Niekerk, Mel Krajden, et al.
JAMA. 2018; 320 (1): 43-52.
https://jamanetwork.com/journals/jama/fullarticle/2686793

Abstract
Importance There is limited information about the relative effectiveness of cervical cancer screening with primary human papillomavirus (HPV) testing alone compared with cytology in North American populations.

Objective To evaluate histologically confirmed cumulative incident cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+) detected up to and including 48 months by primary HPV testing alone (intervention) or liquid-based cytology (control.(
Design, Setting, and Participants Randomized clinical trial conducted in an organized Cervical Cancer Screening Program in Canada. Participants were recruited through 224 collaborating clinicians from January 2008 to May 2012, with follow-up through December 2016. Women aged 25 to 65 years with no history of CIN2+ in the past 5 years, no history of invasive cervical cancer, or no history of hysterectomy; who have not received a Papanicolaou test within the past 12 months; and who were not receiving immunosuppressive therapy were eligible.
Interventions A total of 19 009 women were randomized to the intervention (n = 9552) and control (n = 9457) groups. Women in the intervention group received HPV testing; those whose results were negative returned at 48 months. Women in the control group received liquid-based cytology (LBC) testing; those whose results were negative returned at 24 months for LBC. Women in the control group who were negative at 24 months returned at 48 months. At 48-month exit, both groups received HPV and LBC co-testing.
Main Outcomes and Measures The primary outcome was the cumulative incidence of CIN3+ 48 months following randomization. The cumulative incidence of CIN2+ was a secondary outcome.
Results Among 19 009 women who were randomized (mean age, 45 years [10th-90th percentile, 30-59]), 16 374 (8296 [86.9%] in the intervention group and 8078 [85.4%] in the control group) completed the study. At 48 months, significantly fewer CIN3+ and CIN2+ were detected in the intervention vs control group. The CIN3+ incidence rate was 2.3/1000 (95% CI, 1.5-3.5) in the intervention group and 5.5/1000 (95% CI, 4.2-7.2) in the control group. The CIN3+ risk ratio was 0.42 (95% CI, 0.25-0.69). The CIN2+ incidence rate at 48 months was 5.0/1000 (95% CI, 3.8-6.7) in the intervention group and 10.6/1000 (95% CI, 8.7-12.9) in the control group. The CIN2+ risk ratio was 0.47 (95% CI, 0.34-0.67). Baseline HPV-negative women had a significantly lower cumulative incidence of CIN3+ at 48 months than cytology-negative women (CIN3+ incidence rate, 1.4/1000 [95% CI, 0.8-2.4]; CIN3+ risk ratio, 0.25 [95% CI, 0.13-0.48.([
Conclusions and Relevance Among women undergoing cervical cancer screening, the use of primary HPV testing compared with cytology testing resulted in a significantly lower likelihood of CIN3+ at 48 months. Further research is needed to understand long-term clinical outcomes as well as cost-effectiveness.

Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes

Kasia J. Lipska, Melissa M. Parker, Howard H. Moffet, et al.

JAMA. 2018; 320 (1): 53-62.
https://jamanetwork.com/journals/jama/article-abstract/2685850

Abstract

Importance In clinical trials of patients with type 2 diabetes, long-acting insulin analogs modestly reduced the risk of nocturnal hypoglycemia compared with human neutral protamine Hagedorn (NPH) insulin, but cost 2 to 10 times more. Outcomes in clinical practice may differ from trial results.
Objective To compare the rates of hypoglycemia-related emergency department (ED) visits or hospital admissions associated with initiation of long-acting insulin analogs vs human NPH insulin in patients with type 2 diabetes.

Design, Setting, and Participants A retrospective observational study using data from Kaiser Permanente of Northern California from January 1, 2006, through September 30, 2015. Patients with type 2 diabetes who initiated a long-acting insulin analog or NPH insulin were included and censored at death, loss of health plan coverage, change in insulin treatment, or study end on September 30, 2015.
Exposure Initiation of basal insulin analogs (glargine or detemir) vs NPH insulin.
Main Outcomes and Measures The primary outcome was the time to a hypoglycemia-related ED visit or hospital admission and the secondary outcome was the change in hemoglobin A_{1c} level within 1 year of insulin initiation.
Results There were 25 489 patients with type 2 diabetes who initiated basal insulin therapy (mean age, 60.2 [SD, 11.8] years; 51.9% white; 46.8% female). During a mean follow-up of 1.7 years, there were 39 hypoglycemia-related ED visits or hospital admissions among 1928 patients who initiated insulin analogs (11.9 events [95% CI, 8.1 to 15.6] per 1000 person-years) compared with 354 hypoglycemia-related ED visits or hospital admissions among 23 561 patients who initiated NPH insulin (8.8 events [95% CI, 7.9 to 9.8] per 1000 person-years) (between-group difference, 3.1 events [95% CI, −1.5 to 7.7] per 1000 person-years; $P = .07$). Among 4428 patients matched by propensity score, the adjusted hazard ratio was 1.16 (95% CI, 0.71 to 1.78) for hypoglycemia-related ED visits or hospital admissions associated with insulin analog use. Within 1 year of insulin initiation, hemoglobin A_{1c} level decreased from 9.4% (95% CI, 9.3% to 9.5%) to 8.2% (95% CI, 8.1% to 8.2%) after initiation of insulin analogs and from 9.4% (95% CI, 9.3% to 9.5%) to 7.9% (95% CI, 7.9% to 8.0%) after initiation of NPH insulin (adjusted difference-in-differences for glycemic control, −0.22% [95% CI, −0.09% to −0.37%]).
Conclusions and Relevance Among patients with type 2 diabetes, initiation of a basal insulin analog compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions or with improved glycemic control. These findings suggest that the use of basal insulin analogs in usual practice settings may not be associated with clinical advantages for these outcomes.

Association of the US Department of Justice Investigation of Implantable Cardioverter-Defibrillators and Devices Not Meeting the Medicare National Coverage Determination, 2007-2015

Nihar R. Desai, Paul M. Bourdillon, Craig S. Parzynski, et al.
JAMA. 2018; 320 (1): 63-71.
https://jamanetwork.com/journals/jama/article-abstract/2686795

Abstract
Importance The US Department of Justice (DOJ) conducted an investigation into implantable cardioverter-defibrillators (ICDs) not meeting the Centers for Medicare & Medicaid Services National Coverage Determination (NCD) criteria.
Objective To examine changes in the proportion of initial primary prevention ICDs that did not meet NCD criteria following the announcement of the DOJ investigation at hospitals that reached settlements (settlement hospitals) and those that did not (nonsettlement hospitals).
Design, Setting, and Participants Multicenter, longitudinal, serial cross-sectional analysis of 300 151 initial primary prevention ICDs among Medicare beneficiaries from January 1, 2007, through December 31, 2015, at 1809 US hospitals in the National Cardiovascular Data Registry (NCDR) ICD Registry, of which 452 hospitals (with 99 591 primary prevention ICDs) reached settlements with the DOJ.
Exposures The DOJ investigation announcement in 2010.

Main Outcomes and Measures Proportion of initial primary prevention ICDs not meeting NCD criteria.

Results In January 2007, the proportion of initial ICDs not meeting NCD criteria was 25.8% (95% CI, 24.7% to 26.8%) at settlement hospitals and 22.8% (95% CI, 22.1% to 23.5%) at nonsettlement hospitals ($P < .001$). Over the study period, there was a 62.7% (95% CI, 59.2% to 66.1%) relative decrease and 16.1% (95% CI, 14.8% to 17.5%) absolute decrease in the proportion of ICDs not meeting NCD criteria at settlement hospitals compared with a 53.2% (95% CI, 50.4% to 56.0%) relative decrease and 12.1% (95% CI, 11.2% to 13.0%) absolute decrease in proportion at nonsettlement hospitals ($P < .001$ for both; P for interaction $< .001$). Trends significantly differed between hospital groups only in the period following the announcement of the DOJ investigation (June 2010-June 2011), with larger and more rapid decreases at settlement hospitals (P for interaction $= .01$). Over the study period, there was a 32.8% (95% CI, 29.9% to 35.7%) relative decrease and a 1703 ICDs (95% CI, 1520 to 1886) absolute decrease in the volume of primary prevention ICDs implanted at settlement hospitals compared with a 17.4% (95% CI, 14.8% to 20.0%) relative decrease and a 1495 ICDs (95% CI, 1249 to 1741) absolute decrease in volume at nonsettlement hospitals ($P < .001$ for both; P for interaction $< .001$), with more modest decreases or slight increases in secondary prevention ICD volume. These patterns were similar when examining ICD utilization among non–Medicare beneficiaries.

Conclusions and Relevance From 2007 through 2015, the volume of primary prevention implantable cardioverter-defibrillators and the proportion of devices not meeting the Centers for Medicare & Medicaid Services National Coverage Determination criteria decreased at all hospitals with substantially larger decreases at hospitals that reached settlements in the US Department of Justice investigation. These patterns extended to implantable cardioverter-defibrillators placed in non–Medicare beneficiaries, which were not the focus of the US Department of Justice investigation.

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The Lancet (30 June 2018, Vol. 391, No. 10140)

MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: A randomised, controlled, double-blind, ascending dose and phase 2a study

Philip Ambery, Victoria E Parker, Michael Stumvoll, et al.

The Lancet: Volume 391, No. 10140, p2607–2618, 30 June 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30726-8/fulltext

Summary

Background

Weight loss is often key in the management of obese or overweight patients with type 2 diabetes, yet few treatments for diabetes achieve clinically meaningful weight loss. We aimed to assess the efficacy, tolerability, and safety of treatment with MEDI0382, a balanced glucagon-like peptide-1 and glucagon receptor dual agonist developed to provide glycaemic control and weight loss, in patients with type 2 diabetes.

Methods

This randomised, placebo-controlled, double-blind, combined multiple-ascending dose (MAD) and phase 2a study was done at 11 study sites (hospitals and contract research organisations) in Germany. We enrolled patients aged 18–65 years with controlled type 2

diabetes (glycated haemoglobin A_{1c} [HbA_{1c}] levels of 6·5–8·5% at screening) and a body-mass index between 27 kg/m^2 and 40 kg/m^2. An interactive web-response system was used to randomly assign patients to receive MEDI0382 or placebo. Patients were randomly assigned 2:1 in cohorts A–C and 3:1 in cohorts D and E in the MAD portion of the study, and 1:1 in the phase 2a portion. Randomisation was done by a contracted third-party operator who was not involved in the clinical operations of the study. The pharmacists, participants, and study site personnel involved in treating and assessing participants were masked to treatment allocation. Patients received once-daily subcutaneous injections of the study drug at doses of no more than 300 µg for 22 days or less in the MAD portion of the study, and a dose of no more than 200 µg for 41 days or less in the phase 2a portion. The two primary endpoints of the phase 2a portion were the change from baseline to day 41 in glucose area under the curve at 0–4 h ($AUC_{0–4\ h}$) after a mixed-meal tolerance test (MMTT), assessed in all participants who received at least one dose of study drug and whose measurements were taken at baseline and day 41, and change from baseline in bodyweight, assessed in the intention-to-treat (ITT) population. Safety analyses were done in all participants who received any study drug analysed according to the treatment they received. This study is registered with ClinicalTrials.gov, number NCT02548585.

Findings

Patients were recruited between Dec 9, 2015, and Feb 24, 2017. 61 patients were randomly assigned to the MAD part of the study (42 to MEDI0382 and 19 to placebo). 51 patients were randomly assigned to the phase 2a part, of whom 25 were randomly assigned to MEDI0382 and 26 to placebo. In the phase 2a study, three patients in the MEDI0382 group and one in the placebo group discontinued, all as a result of adverse events. 22 (88%) patients in the MEDI0382 group and 25 (96%) in the placebo group received at least one dose and had measurements taken at baseline and day 41. Glucose $AUC_{0–4\ h}$ post MMTT decreased significantly with MEDI0382 versus placebo (least squares [LS] mean −32·78% [90% CI −36·98 to −28·57] *vs* −10·16% [–14·10 to −6·21], and the mean difference was −22·62% [–28·40 to −16·85]; p<0·0001). In the ITT population, reduction in bodyweight was significantly greater with MEDI0382 than with placebo (LS mean −3·84 kg [90% CI −4·55 to −3·12] *vs* −1·70 kg [–2·40 to −1·01] and mean difference of 2·14 kg [–3·13 to −1·31]; p=0·0008). The proportion of patients who had a treatment-emergent adverse event (TEAE) was similar between treatment groups (22 [88%] of 25 in the MEDI0382 group *vs* 23 [88%] of 26 in the placebo group); gastrointestinal disorders (18 [72%] *vs* 13 [40%]) and decreased appetite (five [20%] *vs* none) occurred more frequently with MEDI0382 than placebo. No participants in the MEDI0382 group had a grade 3 or worse TEAE (*vs* two [8%] in the placebo group).

Interpretation

MEDI0382 has the potential to deliver clinically meaningful reductions in blood glucose and bodyweight in obese or overweight individuals with type 2 diabetes.

Belimumab in kidney transplantation: An experimental medicine, randomised, placebo-controlled phase 2 trial

Gemma D Banham, Shaun M Flint, Nicholas Torpey, et al.

The Lancet: Volume 391, No. 10140, p2619–2630, 30 June 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30984-X/fulltext

Summary

Background

B cells produce alloantibodies and activate alloreactive T cells, negatively affecting kidney transplant survival. By contrast, regulatory B cells are associated with transplant tolerance. Immunotherapies are needed that inhibit B-cell effector function, including antibody secretion, while sparing regulators and minimising infection risk. B lymphocyte stimulator (BLyS) is a cytokine that promotes B-cell activation and has not previously been targeted in kidney transplant recipients. We aimed to determine the safety and activity of an anti-BLyS antibody, belimumab, in addition to standard-of-care immunosuppression in adult kidney transplant recipients. We used an experimental medicine study design with multiple secondary and exploratory endpoints to gain further insight into the effect of belimumab on the generation of de-novo IgG and on the regulatory B-cell compartment.

Methods

We undertook a double-blind, randomised, placebo-controlled phase 2 trial of belimumab, in addition to standard-of-care immunosuppression (basiliximab, mycophenolate mofetil, tacrolimus, and prednisolone) at two centres, Addenbrooke's Hospital, Cambridge, UK, and Guy's and St Thomas' Hospital, London, UK. Participants were eligible if they were aged 18–75 years and receiving a kidney transplant and were planned to receive standard-of-care immunosuppression. Participants were randomly assigned (1:1) to receive either intravenous belimumab 10 mg per kg bodyweight or placebo, given at day 0, 14, and 28, and then every 4 weeks for a total of seven infusions. The co-primary endpoints were safety and change in the concentration of naive B cells from baseline to week 24, both of which were analysed in all patients who received a transplant and at least one dose of drug or placebo (the modified intention-to-treat [mITT] population). This trial has been completed and is registered with ClinicalTrials.gov, NCT01536379, and EudraCT, 2011–006215–56.

Findings

Between Sept 13, 2013, and Feb 8, 2015, of 303 patients assessed for eligibility, 28 kidney transplant recipients were randomly assigned to receive belimumab (n=14) or placebo (n=14). 25 patients (12 [86%] patients assigned to the belimumab group and 13 [93%] patients assigned to the placebo group) received a transplant and were included in the mITT population. We observed similar proportions of adverse events in the belimumab and placebo groups, including serious infections (one [8%] of 12 in the belimumab group and five [38%] of 13 in the placebo group during the 6-month on-treatment phase; and none in the belimumab group and two [15%] in the placebo group during the 6-month follow-up). In the on-treatment phase, one patient in the placebo group died because of fatal myocardial infarction and acute cardiac failure. The co-primary endpoint of a reduction in naive B cells from baseline to week 24 was not met. Treatment with belimumab did not significantly reduce the number of naive B cells from baseline to week 24 (adjusted mean difference between the belimumab and placebo treatment groups −34·4 cells per μL, 95% CI −109·5 to 40·7).

Interpretation

Belimumab might be a useful adjunct to standard-of-care immunosuppression in renal transplantation, with no major increased risk of infection and potential beneficial effects on humoral alloimmunity.

Assessment of functional capacity before major non-cardiac surgery: An international, prospective cohort study

Duminda N Wijeysundera, Rupert M Pearse, Mark A Shulman, et al. on behalf of the METS Study investigators

The Lancet: Volume 391, No. 10140, p2631–2640, 30 June 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31131-0/fulltext

Summary
Background
Functional capacity is an important component of risk assessment for major surgery. Doctors' clinical subjective assessment of patients' functional capacity has uncertain accuracy. We did a study to compare preoperative subjective assessment with alternative markers of fitness (cardiopulmonary exercise testing [CPET], scores on the Duke Activity Status Index [DASI] questionnaire, and serum N-terminal pro-B-type natriuretic peptide [NT pro-BNP] concentrations) for predicting death or complications after major elective non-cardiac surgery.
Methods
We did a multicentre, international, prospective cohort study at 25 hospitals: five in Canada, seven in the UK, ten in Australia, and three in New Zealand. We recruited adults aged at least 40 years who were scheduled for major non-cardiac surgery and deemed to have one or more risk factors for cardiac complications (eg, a history of heart failure, stroke, or diabetes) or coronary artery disease. Functional capacity was subjectively assessed in units of metabolic equivalents of tasks by the responsible anaesthesiologists in the preoperative assessment clinic, graded as poor (<4), moderate (4–10), or good (>10). All participants also completed the DASI questionnaire, underwent CPET to measure peak oxygen consumption, and had blood tests for measurement of NT pro-BNP concentrations. After surgery, patients had daily electrocardiograms and blood tests to measure troponin and creatinine concentrations until the third postoperative day or hospital discharge. The primary outcome was death or myocardial infarction within 30 days after surgery, assessed in all participants who underwent both CPET and surgery. Prognostic accuracy was assessed using logistic regression, receiver-operating-characteristic curves, and net risk reclassification.
Findings
Between March 1, 2013, and March 25, 2016, we included 1401 patients in the study. 28 (2%) of 1401 patients died or had a myocardial infarction within 30 days of surgery. Subjective assessment had 19·2% sensitivity (95% CI 14·2–25) and 94·7% specificity (93·2–95·9) for identifying the inability to attain four metabolic equivalents during CPET. Only DASI scores were associated with predicting the primary outcome (adjusted odds ratio 0·96, 95% CI 0·83–0·99; p=0·03).
Interpretation
Subjectively assessed functional capacity should not be used for preoperative risk evaluation. Clinicians could instead consider a measure such as DASI for cardiac risk assessment.

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The New England Journal of Medicine (28 June 2018, Vol. 378, No. 26)

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer
Maha Hussain, Karim Fizazi, Fred Saad, et al.
N Engl J Med 2018; 378: 2465-2474 June 28, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1800536

Abstract
Background
Men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising prostate-specific antigen (PSA) level are at high risk for metastasis. We hypothesized that

enzalutamide, which prolongs overall survival among patients with metastatic, castration-resistant prostate cancer, would delay metastasis in men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising PSA level.

Methods

In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. The primary end point was metastasis-free survival (defined as the time from randomization to radiographic progression or as the time to death without radiographic progression).

Results

A total of 1401 patients (median PSA doubling time, 3.7 months) underwent randomization. As of June 28, 2017, a total of 219 of 933 patients (23%) in the enzalutamide group had metastasis or had died, as compared with 228 of 468 (49%) in the placebo group. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; P<0.001). The time to the first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; P<0.001; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; P<0.001; progression occurred in 22% vs. 69% of patients). At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo.

Conclusions

Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo. Adverse events were consistent with the established safety profile of enzalutamide.

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, Parameswaran Nair, Guy Brusselle, et al.

N Engl J Med 2018; 378: 2475-2485 June 28, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1804093

Abstract

Background

Dupilumab is a fully human anti–interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. Its effectiveness in reducing oral glucocorticoid use in patients with severe asthma while maintaining asthma control is unknown.

Methods

We randomly assigned 210 patients with oral glucocorticoid–treated asthma to receive add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe

exacerbation rates and the forced expiratory volume in 1 second (FEV1) before bronchodilator use were also assessed.

Results

The percentage change in the glucocorticoid dose was −70.1% in the dupilumab group, as compared with −41.9% in the placebo group (P<0.001); 80% versus 50% of the patients had a dose reduction of at least 50%, 69% versus 33% had a dose reduction to less than 5 mg per day, and 48% versus 25% completely discontinued oral glucocorticoid use. Despite reductions in the glucocorticoid dose, in the overall population, dupilumab treatment resulted in a severe exacerbation rate that was 59% (95% confidence interval [CI], 37 to 74) lower than that in the placebo group and resulted in an FEV1 that was 0.22 liters (95% CI, 0.09 to 0.34) higher. Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%). Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%).

Conclusions

In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1. Transient eosinophilia was observed in approximately 1 in 7 dupilumab-treated patients.

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

Mario Castro, Jonathan Corren, Ian D. Pavord, et al.

N Engl J Med 2018; 378:2486-2496 June 28, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1804092

Abstract

Background

Dupilumab is a fully human anti–interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. We assessed its efficacy and safety in patients with uncontrolled asthma.

Methods

We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and dupilumab safety were also assessed.

Results

The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks. At week 12, the FEV1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose. Among patients with a blood eosinophil count of 300 or more per cubic millimeter, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower-dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6); similar results

were observed with the higher dose. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo.

Conclusions

In this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. Hypereosinophilia was observed in some patients.

Combined Analysis of Asthma Safety Trials of Long-Acting β2-Agonists

William W. Busse, Eric D. Bateman, Arthur L. Caplan, et al.
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https://www.nejm.org/doi/full/10.1056/NEJMoa1716868

Abstract

Background

Safety concerns regarding long-acting β2-agonists (LABAs) in asthma management were initially identified in a large postmarketing trial in which the risk of death was increased. In 2010, the Food and Drug Administration (FDA) mandated that the four companies marketing LABAs for asthma perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone in adolescents (12 to 17 years of age) and adults. In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to provide a final combined analysis of the four trials.

Methods

As members of the joint oversight committee, we performed a combined analysis of the four trials comparing an inhaled glucocorticoid plus a LABA (combination therapy) with an inhaled glucocorticoid alone. The primary outcome was a composite of asthma-related intubation or death. Post hoc secondary outcomes included serious asthma-related events and asthma exacerbations.

Results

Among the 36,010 patients in the intention-to-treat study, there were three asthma-related intubations (two in the inhaled-glucocorticoid group and one in the combination-therapy group) and two asthma-related deaths (both in the combination-therapy group) in 4 patients. In the secondary analysis of serious asthma-related events (a composite of hospitalization, intubation, or death), 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and 119 of 18,004 patients (0.66%) in the combination-therapy group had at least one composite event (relative risk in the combination-therapy group, 1.09; 95% confidence interval [CI], 0.83 to 1.43; P=0.55); 2100 patients in the inhaled-glucocorticoid group (11.7%) and 1768 in the combination-therapy group (9.8%) had at least one asthma exacerbation (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001).

Conclusions

Combination therapy with a LABA plus an inhaled glucocorticoid did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma exacerbations.

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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/
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

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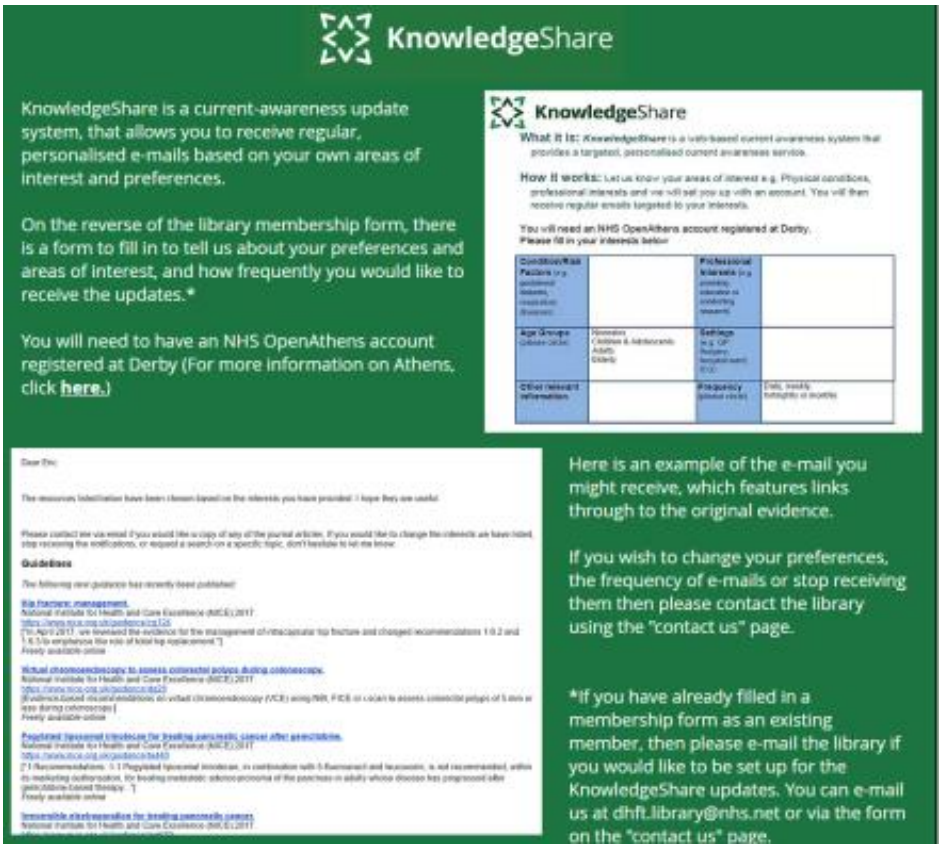

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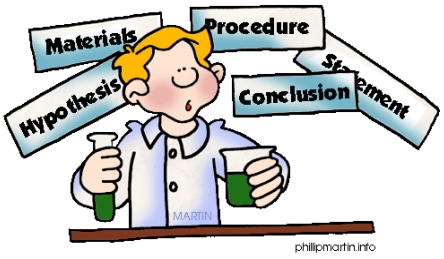

For more information please go to the Training pages on our website, http://www.derbyhospitalslibrary.co.uk/training, or email suzanne.toft@nhs.net

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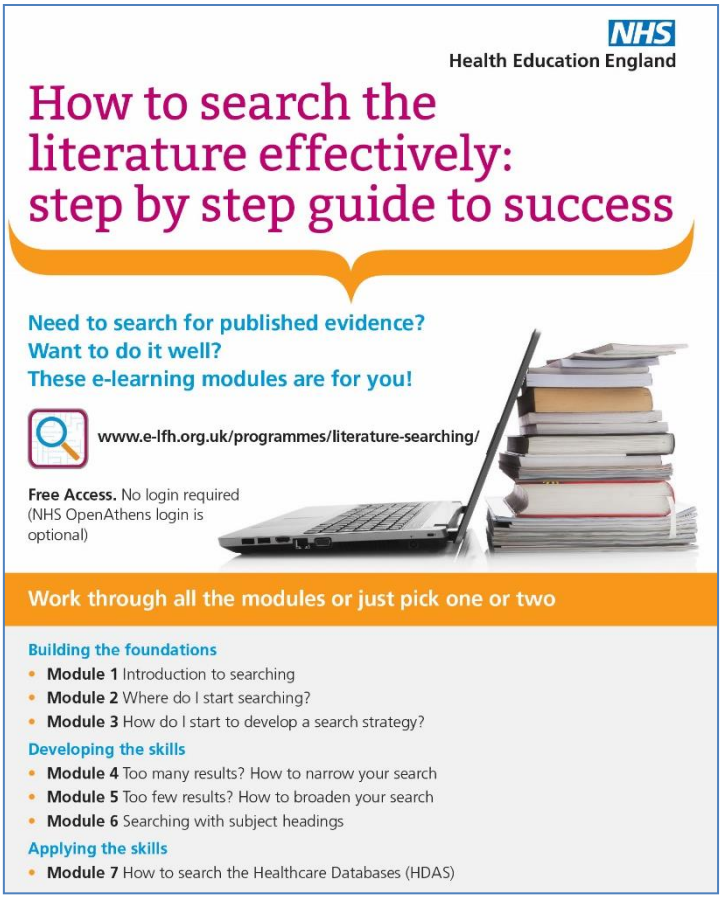

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