

2019

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RECUEIL DES PUBLICATIONS DU CHU UCL NAMUR

N°5 - DEUXIÈME QUADRIMESTRE 2019

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SUPPLÉMENT
PREMIER QUADRIMESTRE 2019

Health and frailty among older spousal caregivers: an observational cohort study in Belgium.

Potier F, Degryse JM, Bihin B, Debacq-Chainiaux F, Charlet-Renard C, Martens H, de Saint-Hubert M.

Références	Doi	IF
BMC Geriatr. 2018 Nov 26;18(1):291	10.1186/s12877-018-0980-3	2,866

Abstract

BACKGROUND: Among older couples, spouses are first in line to provide care, and they are key elements in the home support of dependent older persons. In this context, ensuring the health of these older spousal caregivers should be an important issue for all of the providers who care for older adults. The aim of this study was to longitudinally assess the health of older spousal caregivers considering frailty, nutrition, cognition, physical performance and mood disorders.

METHODS: In this longitudinal, observational cohort study, participants were assessed at home in Wallonia, Belgium. At baseline, 82 community-dwelling spouses of older patients with cognitive deficits or functional impairment were assessed; 78 caregivers were assessed at follow-up (16 months). The clinical instruments used included Frailty Phenotype (Fried), the Mini Nutritional Assessment-short form (MNA-SF), Short Physical Performance Battery (SPPB), Geriatric Depression Scale (GDS-15), clock drawing test, medications, Zarit Burden Index (ZBI), and Caregiver Reaction Assessment (CRA). Biological assessments included plasma interleukin-6 (IL-6), ultrasensitive C-reactive protein (CRP), cortisol, albumin and insulin growth factor-1 (IGF-1).

RESULTS: Among caregivers, 54% were women, and the mean age was 80 years. Among care-receivers, 83% had cognitive impairment. Caregivers were more likely to be in a pre-frail stage. In one-third of the caregivers, the frailty status worsened. Transitions were observed between each of the states, except from frail to robust. In contrast to frailty, items including nutrition, cognitive status, SPPB and mood assessments were stable over time, with approximately 70% of the caregivers not experiencing significant change at follow-up. Caregiver experiences assessed with the Zarit Burden Interview and CRA were relatively stable over 16 months.

CONCLUSIONS: Many caregivers of geriatric patients are spouses who are old themselves. A failure in the health of the caregiver may anticipate an undesired care breakdown. Caregiver health and its determinants should be explored in future longitudinal studies that cover a longer time period

Mots-clefs

Biomarkers; Caregiving; Cognition; Frailty; Nutrition

Incidence and Predictors of Success of Adalimumab Dose Escalation and De-escalation in Ulcerative Colitis: a Real-World Belgian Cohort Study.

Van de Vondel S, Baert F, Reenaers C, Vanden Branden S, Amininejad L, Dewint P, Van Moerkercke W, **Rahier JF**, Hindryckx P, Bossuyt P, Ferrante M; Belgian IBD Research and Development (BIRD).

Références

Doi

IF

Inflamm Bowel Dis. 2018 Apr 23;24(5):1099-1105

10.1093/ibd/izx103

4,005

Abstract

BACKGROUND: Adalimumab (ADM) has been shown efficacious in ulcerative colitis (UC). In randomized controlled trials, dose escalation from 40 mg ADM every other week to 40 mg every week was required in 20%-25% of patients within 1 year. Real-life data suggest higher escalation rates. Attempts for dose de-escalation have not been studied yet. We assessed the need for, outcome of, and predictors of dose escalation and de-escalation in a large retrospective cohort of UC patients treated with ADM.

METHODS: We included 231 consecutive patients from 10 Belgian centers initiating ADM treatment for active UC before September 1, 2015 (follow-up ≥ 1 year in each patient). We performed detailed chart review to identify variables associated with short-term clinical benefit (based on physician global assessment and absence of rectal bleeding at week 10), success of dose escalation, and dose de-escalation. Backward Cox regression and Wald Logistic regression were used to identify predictive variables.

RESULTS: Short-term clinical benefit was achieved in 101 patients (44%) and was less frequent in infliximab failures [37% vs 50%, Odds ratio 0.57 (95% CI 0.34-0.97), $P = 0.038$]. After a median of 2.8 (1.7-5.1) months, 164 patients (71%) needed ADM discontinuation ($n = 35$, 15%) or dose escalation ($n = 129$, 56%). Dose escalation was successful in 77/129 (60%). Dose de-escalation was attempted in 71% (55/77) after a median of 4.3 (2.9-7.2) months and was successful in 80% (43/54).

CONCLUSIONS: In this cohort, 56% of patients with UC required ADM dose escalation with a 60% success rate. Of note, most patients could be successfully de-escalated later on.

Mots-clefs

Associating liver partition and portal vein ligation for staged hepatectomy : establishment of an animal model with insufficient liver remnant.

Dili A, Lebrun V, Bertrand C, Leclercq I.

Références	Doi	IF
Laboratory Invest 2019 Jan;99(5):698-707	10.1038/s41374-018-0155-z	4,857

Abstract

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) allows extended hepatectomy in patients with an extremely small future liver remnant (FLR). Current rodent models of ALPPS do not include resection resulting in insufficient-for-survival FLR, or they do incorporate liver mass reduction prior to ALPPS. Differences in FLR volume and surgical procedures could bias our understanding of physiological and hemodynamic mechanisms. We aimed to establish a rat ALPPS model with minimal FLR without prior parenchymal resection. In rodents, the left median lobe (LML) represents 10% of total liver. Partial hepatectomy (PHx) sparing LML and pericaval parenchyma represents our reference 87% resection. The first step in the procedure is either portal vein ligation (PVL) corresponding to ligation of all but the LML portal branches, or PVL with transection between the left and right median lobe segments (PVLT), and is defined as ALPPS stage-1. Second, ligated lobes were removed: PVL-PHx represents a conventional 2-stage hepatectomy, while PVLT followed by PHx is a strict reproduction of human ALPPS. In Group A, liver hypertrophy was analyzed after PVL (n=38), PVLT (n=47), T (n=10), and sham (n=10); In group B, mortality and FLR hypertrophy was assessed after PHx (n=42), Sham-PHx (n=6), PVL-PHx (n=37), and PVLT-PHx (n=45). In group A, PVLT induced rapid FLR hypertrophy compared to PVL ($p < 0,05$). Hepatocyte proliferation was higher in PVLT remnants ($p < 0,05$). In group B, PHx had a 5-day mortality rate of 84%. Sham operation prior to PHx did not improve survival ($p = 0,23$). In both groups, major fatalities occurred within 48 h after resection. PVL or PVLT prior to PHx reduced mortality to 33.3% ($p = 0,007$) or 25% ($p = 0,0002$) respectively, with no difference between the 2 two-stage procedures ($p = 0,6$). 7-day FLR hypertrophy was higher after the PVLT-PHx compared to PVL-PHx and PHx ($p = 0,024$). Our model reproduces human ALPPS with FLR that is insufficient for survival without liver resection prior to the stage-1 procedure. It offers an appropriate model for analyzing the mechanisms driving survival rescue and increased hypertrophy.

Mots-clefs

Giant pulmonary artery aneurysms. Case report and proposal of management algorithm.

Radermecker A, Stiennon L, **Leroux A**, Sooknunden M, Duysinx B, Guiot J, Davin L, Sakalihan N, Radermecker MA, Defraigne JO.

Références

Doi

IF

Rev Med Liege. 2019 Feb;74(2):90-94.

0,07

Abstract

Pulmonary artery aneurysm is a rare and multiform pathology related to multiple etiologies and therefore different pathophysiological mechanisms. Delineating homogenous sub-groups is a pre-requisite to refine medico-surgical management. The case of a giant PAA without pulmonary hypertension but associated to a dysplastic pulmonary valve is reported. This association could be in some instances the result of a congenital anomaly in the development of both the pulmonary valve and the root creating the conditions for further development of a pulmonary artery aneurysm. Whilst minor forms are usually asymptomatic, they can lead to lethal complications in huge sizes and are frequently associated via pulmonary valve insufficiency to right ventricular dysfunction. This specific association is discussed and a diagnostic algorithm for nosologic classification and management is proposed.

Mots-clefs

Aneurysm ; Dysplastic pulmonary valve; Pulmonary artery

Intrarenal activation of adaptive immune effectors is associated with tubular damage and impaired renal function in lupus nephritis.

Pamfil C, Makowska, De Groof A, Tilman G, Babaei S, Galant C, **Montigny P**, Demoulin N, Jadoul M, Aydin S, Lesche R, McDonald F, Houssiau FA, Lauwerys BR.

Références	Doi	IF
<i>Ann Rheum Dis.</i> 2018 Dec;77(12):1782-1789	10.1136/annrheumdis-2018-213485	14,299

Abstract

OBJECTIVES: Chronic renal impairment remains a feared complication of lupus nephritis (LN). The present work aimed at identifying mechanisms and markers of disease severity in renal tissue samples from patients with LN.

METHODS: We performed high-throughput transcriptomic studies (Illumina HumanHT-12 v4 Expression BeadChip) on archived kidney biopsies from 32 patients with LN and eight controls (pretransplant donors). Histological staging (glomerular and tubular scores) and immunohistochemistry experiments were performed on the same and on a replication set of 37 LN kidney biopsy samples.

RESULTS: A group of LN samples was identified by unsupervised clustering studies based on their gene expression features, that is, the overexpression of transcripts involved in antigen presentation, T and B cell activation. These samples were characterised by a significantly lower estimated glomerular filtration rate (eGFR) at the time of biopsy (To) compared with the other systemic lupus erythematosus samples. Yet, apparent disease duration at To, double-stranded DNA antibody titres at To and other relevant characteristics (serum C3, proteinuria, histological scores, numbers of previous flares) were not different between groups. Immunohistochemistry studies confirmed the association between interstitial infiltration by adaptive immune effectors and decreased renal function in the same and in a replication group of LN kidney biopsies. This was associated with transcriptomic, histological and immunohistochemical evidence of renal tubular cell involvement.

CONCLUSION: Interstitial infiltration of LN kidney biopsies by adaptive immune effectors is associated with impaired renal tubular cell function and decreased eGFR. These results open new perspectives in evaluating and treating patients with LN, focusing on intrarenal mechanisms of immune cell activation.

Mots-clefs

T cells; lupus nephritis; systemic lupus erythematosus

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DU CHU UCL NAMUR
N°5 - DEUXIÈME QUADRIMESTRE 2019



MAI

Andexanet alfa for the reversal of factor Xa inhibitors.

Favresse J, Hardy M, van Dievoet MA, Sennesael AL, Douxfils J, Samama CM, Vornicu O, Dincq AS, Lessire S, Mullier F

Références	Doi	IF
Expert Opin Biol Ther. 2019 May;19(5):387-397	10.1080/14712598.2019.1599355	3,974

Abstract

Andexanet alfa is a recombinant modified factor Xa protein that has been developed to reverse factor Xa inhibitors. Since May 2018, the FDA has approved its utilization in patients treated with apixaban and rivaroxaban in case of life-threatening or uncontrolled bleeding. On 28 of February 2019, the Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a conditional marketing authorization for andexanet alfa in Europe. Area covered: The authors provide an overview of andexanet alfa development and its pharmacokinetic and pharmacodynamic properties. The results of the clinical phase III trial ANNEXA as well as current limitations related to andexanet alfa are also discussed. Expert opinion: Although phase I and II studies have proven that andexanet alfa can be effective in reversing the effect of factor Xa inhibitors, its efficacy in major bleeding patients has only been shown for apixaban and rivaroxaban, without any comparator group. Well-designed studies comparing the efficacy and safety of andexanet alfa to other reversal strategies are required to confirm preliminary data. The benefit of andexanet alfa in specific settings needs to be investigated and its use in clinical practice needs to be facilitated by the implementation of international guidelines.

Mots-clefs

ANNEXA; Andexanet alfa; DOACs; antidote; factor Xa; major bleeding; reversal agents

Azithromycin during Acute COPD Exacerbations Requiring Hospitalization (BACE): a Multicentre, Randomized, Double-blind, Placebo-controlled Trial.

Vermeersch K, Gabrovska M, Aumann J, Demedts IK, Corhay JL, **Marchand E**, Slabbynck H, Haenebalcke C, Haerens M, Hanon S, Jordens P, Peché R, Fremault A5, Lauwerier T, Delporte A, Vandenberg B, Willems R, Everaerts S, Belmans A, Bogaerts K, Verleden GM, Troosters T, Ninane V, Brusselle GG, Janssens W; BACE trial investigators.

<i>Références</i>	<i>Doi</i>	<i>IF</i>
<i>Am J Respir Crit Care Med. 2019 May 3. [Epub ahead of print]</i>	<i>10.1164/rccm.201901-0094OC</i>	<i>16,49</i>

Abstract

RATIONALE: Azithromycin prevents acute exacerbations in COPD (AECOPD); however, its value in the treatment of AECOPD requiring hospitalization is yet to be defined.

OBJECTIVE:

We investigated whether a 3-month intervention with low-dose azithromycin could decrease treatment failure (TF) when initiated at hospital admission and added to standard care.

METHODS: In an investigator-initiated, multi-centre, randomized, double-blind, placebo-controlled trial, patients hospitalized for an AECOPD, with a smoking history of ≥ 10 pack-years and ≥ 1 exacerbation in the previous year, were randomized (1:1) within 48-hours of admission to azithromycin or placebo. The study drug (500mg/day for 3days) was administered on top of a standardized acute treatment of systemic corticosteroids and antibiotics, and subsequently continued for 3 months (3m) (250mg/2days). Patients were followed-up for 6m thereafter. Time-to-first event analyses evaluated the TF rate within 3m as a novel primary endpoint in the intention-to-treat population, with TF defined as the composite of treatment intensification with medication (TI), step-up in hospital care or readmission for respiratory reasons (SH) or all-cause mortality.

MAIN RESULTS: 301 patients were randomized to azithromycin (n=147) or placebo (n=154). The TF rate within 3m was 49% in the azithromycin and 60% in the placebo group (HR=0.73; 95%CI 0.53-1.01; p=0.0526). TI, SH and mortality rates within 3m were 47% vs 60% (p=0.0272), 13% vs 28% (p=0.0024) and 2% vs 4% (p=0.5075), respectively. Clinical benefits were lost 6m after withdrawal.

CONCLUSIONS: 3m of azithromycin for AECOPD requiring hospitalization may significantly reduce TF during the highest risk period. Prolonged treatment seems needed to maintain clinical benefits. Clinical trial registration available at www.clinicaltrials.gov, ID NCT02135354.

Mots-clefs

Composite; Macrolide; Readmission; Time-to-event; Treatment failure

Assessment of the analytical performances and sample stability on ST Genesis system using the STG-DrugScreen application.

Douxfls J, Morimont L, Bouvy C, de Saint-Hubert M, Devalet B, Devroye C, Dincq AS, Dogné JM, Guldenpfennig M, Baudar J, Larock AS, Lessire S, Mullier F

Références	Doi	IF
<i>J Thromb Haemost.</i> 2019 May. [Epub ahead of print]	10.1111/jth.14470	4,662

Abstract

BACKGROUND: Thrombin generation testing has been used to provide information on the coagulation phenotype of patients. The most used technique is the calibrated automated thrombogram (CAT) but it suffers from a lack of standardization preventing its implementation in routine. The ST Genesis is a new analyzer designed to assess thrombin generation based on the same principle as the CAT. Unlike the CAT system, the ST Genesis is a benchtop fully automated analyzer, able to perform the analyses individually and not by batch, with strict control of variables like temperature and volumes, ensuring, theoretically, a maximal reproducibility.

OBJECTIVES: This study aimed at assessing the performance of the STG[®]-DrugScreen application on the ST Genesis analyzer. We also aimed at exploring stability of plasma samples after freezing and defining a reference normal range.

RESULTS: Results demonstrated the excellent inter-experiment precision of the ST Genesis and confirmed that the use of a reference plasma helps reducing the inter-experiments variability. Stability revealed that plasma samples are stable for at least 11 months at -70°C or below, except for those containing low molecular weight heparins which have to be tested within 6 months. Freezing had no impact on the majority of thrombin generation parameters except on time-to-peak.

CONCLUSIONS: Our results suggest an easy implementation of thrombin generation with the use of ST Genesis in the routine laboratory. This will facilitate the design of multicentric studies and enable the establishment of reliable and evidence-based thresholds, which may improve the management of patients treated with anticoagulants. This article is protected by copyright. All rights reserved.

Mots-clefs

Anticoagulants; Blood coagulation tests; Clinical laboratory techniques; Normal range; Reproducibility

Hypoxia protects the liver from Small For Size Syndrome: a lesson learned from the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure in rats.

Dili A, Bertrand C, Lebrun V, Pirlot B, Leclercq IA.

Références	Doi	IF
<i>Am J Transplant.</i> 2019 May 7. [Epub ahead of print]	10.1111/ajt.15420.	6,493

Abstract

Portal hyperperfusion and «dearterialization» of the liver remnant are the main pathogenic mechanisms for Small For Size syndrome (SFSS). ALPPS induces rapid remnant hypertrophy. We hypothesized similar increase in portal pressure/flow into the future liver remnant in ALPPS and SFSS-setting hepatectomies. In a rodent model, ALPPS was compared to SFSS-setting hepatectomy. We assessed mortality, remnant hypertrophy, hepatocyte proliferation, portal and hepatic artery flow, hypoxia-induced response and liver sinusoidal morphology. SFSS-hepatectomy rats were subjected to local (hepatic artery ligation) or systemic (Dimethyloxalylglycine) hypoxia. ALPPS prevented mortality in SFSS-setting hepatectomies. Portal hyperperfusion per liver mass was similar in ALPPS and SFSS. Compared to SFSS, efficient arterial perfusion of the remnant was significantly lower in ALPPS causing pronounced hypoxia confirmed by pimonidazole immunostaining, activation of hypoxia sensors and up-regulation of neo-angiogenic genes. Liver sinusoids, larger in ALPPS, collapsed in SFSS. Induction of hypoxia in SFSS reduced mortality. Hypoxia had no impact on hepatocyte proliferation but contributed to the integrity of sinusoidal morphology. ALPPS hemodynamically differ from SFSS by a much lower arterial flow in ALPPS's FLR. We show that the ensuing hypoxic response is essential fo

Mots-clefs

Weekly carboplatin plus neoadjuvant anthracycline-taxane-based regimen in early triple-negative breast cancer: a prospective phase II trial by the Breast Cancer Task Force of the Belgian Society of Medical Oncology (BSMO).

Fontaine C, Renard V, Van den Bulk H, **Vuylsteke P**, Glorieux P, Dopchie C, Decoster L, Vanacker L, de Azambuja E, De Greve J, Awada A, Wildiers H

Références

Breast Cancer Res Treat. 2019 May 8.
[Epub ahead of print]

Doi

10.1007/s10549-019-05259-z

IF

3,940

Abstract

AIM: To evaluate the pCR rate and toxicity of the addition of weekly carboplatin (Cp) to paclitaxel (wP) and dose-dense (dd) epirubicin/cyclophosphamide (EC) in an open-label phase II study in TNBC patients.

METHODS: Patients were included if they had stage II and III TNBC and received wP (80 mg/m²/week) concurrent with weekly Cp (AUC = 2) for 12 weeks, followed by bi-weekly epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) plus granulocyte colony-stimulating factor (G-CSF) for four cycles, followed by surgery. The primary endpoint was the rate of pCR [(ypTo/isypNo)]. Secondary endpoints included safety and drug delivery.

RESULTS: Sixty-three eligible patients were included. Median age was 51 years (range 29-74); 88.9% had stage II disease, 46% were clinically node positive, and 77.8% had grade 3 tumors. Fifty-four percent achieved a pCR. Twelve percent missed two or more doses of wP, whereas at least two cycles of EC were missed in 9.5%. The rate of tolerance without delays or dose reductions is very low (16%). Sixty-two percent had G_{3/4} neutropenia. Febrile neutropenia occurred in 18 patients of which more than eighty percent occurred during EC despite primary prophylaxis with G-CSF. Thrombocytopenia grade 3/4 was noticed in 11 pts. Three patients developed grade 3 peripheral neuropathy.

CONCLUSION: The addition of weekly carboplatin to neoadjuvant paclitaxel and dd EC leads to a pCR rate comparable to prior studies (54%). However, hematological toxicity and febrile neutropenia rate was unexpectedly high. Future investigations could focus on reversing the sequence, which may lead to better hematological tolerability.

Mots-clefs

Neoadjuvant chemotherapy; Phase 2 trial; Triple-negative early breast cancer; Weekly carboplatin and paclitaxel

Clotting test results correlate better with DOAC concentrations when expressed as a «Correction Ratio»; results before/after extraction with the DOAC Stop reagent.

Exner T, Favresse J, Lessire S, Douxfils J, Mullier F.

Références

Doi

IF

Thromb Res. 2019 Jul;179:69-72.

10.1016/j.thromres.2019.04.028

3,266

Abstract

INTRODUCTION: Clotting test results are currently not useful for estimating direct oral anti-coagulant (DOAC) concentrations because baseline results vary. DOAC Stop is a DOAC extracting agent with no effect on clotting factors. We investigated if aPTT (activated partial thromboplastin time) and dRVVT (dilute Russells viper venom time) results might correlate better with DOAC concentrations if results after DOAC extraction were used to estimate a «before/after» value (Correction Ratio).

MATERIALS AND METHODS: We used activated partial thromboplastin time (aPTT, PTT-LA) and dilute Russells viper venom time clotting test (dRVVT) results previously recorded on DOAC patient plasmas (25 dabigatran, 15 apixaban, 19 rivaroxaban) without known thrombotic risk factors before and after DOAC extraction. DOAC concentrations had been determined by standard chromogenic assays.

RESULTS: Correlations between aPTT and dabigatran, apixaban, and rivaroxaban concentrations were initially poor (0.64, 0.15 and 0.39 respectively). However, they improved significantly to 0.94, 0.89 and 0.80 when the ratios of initial aPTT to the aPTT obtained after DOAC extraction were plotted against DOAC concentration. Still better correlations (0.99, 0.97, 0.95) and much higher sensitivities to the DOACs were obtained when dRVVT (LA Confirm) tests were used following this procedure on the same samples.

CONCLUSIONS: The correlations of aPTT and dRVVT tests with DOAC concentrations were significantly improved by using the ratio of result «before» to those «after» DOAC extraction. The results indicate that dRVVT (especially LA Confirm) and similar tests might be useful for determining DOAC concentrations more reliably and with better sensitivity than currently possible with clotting tests.

Mots-clefs

Activated partial thromboplastin time (aPTT); Apixaban; Correction Ratio; DOAC Stop™; DOACs; Dabigatran; Dilute Russells viper venom time (dRVVT); Rivaroxaban

Prognostic impact of tumor growth velocity in head and neck squamous cell carcinoma treated by radiotherapy: A pilot study.

Delahaut G, Témam S, Ambroise J, Tao Y, Janot F, Van der Vorst S.

Références

Doi

IF

Head Neck. 2019 May 14 [Epub ahead of print]

10.1002/hed.25789

2,442

Abstract

BACKGROUND: When a patient is seen with a newly diagnosed oropharyngeal squamous cell carcinoma, it remains unclear to the treating physicians how fast the tumor growth rate is.

METHODS: From patients with oropharynx squamous cell carcinoma treated by radiotherapy, the investigators selected comparable diagnostic CT-scan (DiCT) and radiotherapy planning CT-scan (RtCT). Tumor and pathological lymph node volumes were measured in order to calculate tumor progression.

RESULTS: From the selection of 19 patients, the mean absolute tumor progression rate was 0.23 ± 0.2 cm³ /d and mean relative progression rate was $1.84 \pm 1.64\%$ /d. Mean tumor doubling time is 286 days (range 7-1282 days), demonstrating a wide range of tumor growth pattern. Significant tumor progression (>20%) between DiCT and RtCT was shown in 73% of patients, and 53% of the patients were seen a tumor progression of >50% within a mean waiting time of 42.1 days. Kaplan-Meier curves showed a non-significant link between fast progression tumors (>1%/d) and higher risk of recurrence (HR: 2.2; P = .23).

CONCLUSIONS: Tumor progression can be assessed based on DiCT and RtCT. Treatment delay should be avoided at all cost. Different growth patterns were evidenced. For the fast-growing tumors subgroup, pejorative clinical outcomes were suggested. Prospective studies are needed to confirm a link between fast-growing tumors and higher risk for recurrence.

Mots-clefs

oropharynx carcinomas; progression; tumor growth

Age-related morphometric changes of the tidemark in the ovine stifle.

Hontoir F, Pirson R, Simon V, Clegg P, **Nisolle JF**, Kirschvink N, Vandeweerd JE.

Références	Doi	IF
<i>Anat Histol Embryol.</i> 2019 Jul;48(4):366-374	10.1111/ahe.12449	0,657

Abstract

Though the ovine stifle is commonly used to study osteoarthritis, there is limited information about the age-related morphometric changes of the tidemark. The objective of this study was to document the number of tidemarks in the stifle of research sheep without clinical signs of osteoarthritis and of various ages (n = 80). Articular cartilage of the medial and lateral tibial condyles and of the medial and lateral femoral condyles was assessed by histology: (a) to count the number of tidemark; and (b) to assess the OARSI (Osteoarthritis Research Society International) score for structural changes of cartilage. The number of tidemarks varied between anatomical regions, respectively, from 4.2 in the medial femoral condyle to 5.0 in the lateral tibial condyle. The axial part showed a significant higher number of tidemarks than the abaxial part, for all regions except the medial tibial condyle. Whilst the tidemark count strongly correlated with age (Spearman's correlation coefficient = 0.70; 95% confidence interval (95% CI): 0.67-0.73; $p < 0.0001$), the OARSI score was weakly correlated with age in our cohort of sheep (Spearman's correlation coefficient = 0.25; 95% CI: 0.19-0.30; $p < 0.0001$). Interestingly, no tidemark was seen in the three animals aged 6 months. Our data indicate that the number of tidemarks increases with age and vary with anatomical region. The regional variation also revealed a higher number of tidemarks in the tibia than in the femur. This could be attributed to the local variation in cartilage response to strain and to the difference in chondrocyte biology and density.

Mots-clefs

ageing; cartilage; knee; osteoarthritis; sheep

Erratum to «Percutaneous portal vein recanalization using self-expandable nitinol stents in patients with non-cirrhotic non-tumoral portal vein occlusion» [Diagn. Interv. Imaging 100 (2019) 147-156].

Marot A, Vieira Barbosa J, Duran R, Deltenre P, Denys A.

Références

Doi

IF

Anat Histol Embryol. 2019 Jul;48(4):366-374

10.1016/j.diii.2019.04.005

0,657

Abstract

Percutaneous portal vein recanalization using self-expandable nitinol stents in patients with non-cirrhotic non-tumoral portal vein occlusion. [Diagn Interv Imaging. 2019]

Mots-clefs

Toward standardization of assays measuring extracellular vesicle-associated tissue factor activity.

Nieuwland R, Gardiner C, Dignat-George F, Mullier F, Mackman N, Woodhams B, Thaler J.

Références

Doi

IF

J Thromb Haemost. 2019 May 16 [Epub ahead of print]

10.1111/jth.14481

4,662

Abstract

INTRODUCTION: Secondary acute myeloid leukemia (sAML) remains a therapeutic challenge. In elderly patients with AML, it is unclear whether sAML displays an inferior outcome compared with de novo AML.

PATIENTS AND METHODS: We studied AML with an antecedent of hematologic disease, treatment-related AML, or AML occurring concurrently to another malignancy in a single-center cohort of patients aged 70 and older with AML. The study included 169 patients who were compared with a cohort of patients with de novo AML, without any prior history of malignant disorders, seen during the same period of time.

RESULTS: Hematologic antecedents or presence of prior/concurrent solid malignancy did not impact complete remission rates and overall survival. In multivariate analysis, sAML appeared without independent prognostic value in the elderly.

CONCLUSION: Our results support that sAML and de novo AML in elderly patients are not prognostically distinct entities. They should therefore not be considered separately when investigating outcomes and new treatment strategies.

Mots-clefs

Chemotherapy; Hypomethylating agents; Prognosis; Treatment; Treatment-related leukemia

Dementia, End of Life, and Euthanasia: A Survey Among Dementia Specialists Organized by the Belgian Dementia Council.

Picard G, Bier JC, Capron I, De Deyn PP, Deryck O, Engelborghs S, Hanseeuw B, Lemper JC, **Mormont E**, Petrovic M, Salmon E, Segers K, Sieben A, Thiery E, Ventura M, Versijpt J, Ivanoiu A.

Références

Doi

IF

J Alzheimers Dis. 2019;69(4):989-1001

10.3233/JAD-181277

3,920

Abstract

BACKGROUND: Palliative care and Advance Care Planning (ACP) are increasingly recommended for an optimal management of late-stage dementia. In Belgium, euthanasia has been decriminalized in 2002 for patients who are «mentally competent» (interpreted as non-demented). It has been suggested that advance directives for euthanasia (ADE) should be made possible for dementia patients.

OBJECTIVE: This study presents the results of an internet survey among Belgian dementia specialists.

METHODS: In 2013, the Belgian Dementia Council (BeDeCo) organized a debate on end of life decisions in dementia. Participants were medical doctors who are specialists in the dementia field. After the debate, an anonymous internet survey was organized. The participation rate was 55%. The sample was representative of the BeDeCo members.

RESULTS: The results showed consensus in favor of palliative care and ACP, although ACP is not systematically addressed in practice. Few patients with dementia have requested euthanasia, but for those who did the participants had agreed to implement it for some patients. A majority of participants (94%) believe that most patients and their families are poorly informed about euthanasia. Although most participants (77%) said they approved the Law on euthanasia, 65% said they were against an extension of the Law to allow ADE for dementia.

CONCLUSION: Palliative care and ACP are clearly accepted by professionals, although a gap between recommendation and practice remain. Euthanasia is a much more debated issue, even if a majority of professionals are, in principle, in favor of the current Law and seem to disapprove with a Law change allowing ADE for dementia. A better education for both health professionals and the lay public will be a key element in the future.

Mots-clefs

Advance directive; Alzheimer's disease; dementia; end of life; euthanasia; expert opinion

The effect of community dialogues and sensitization on patient reporting of adverse events in rural Uganda: Uncontrolled before-after study.

Ndagije HB, Manirakiza L, Kajungu D, Galiwango E, Kusemererwa D, Olsson S, **Spinewine A**, Speybroeck N.

Références

Doi

IF

PLoS One. 2019 May 9;14(5):e0203721

10.1371/journal.pone.0203721

2,766

Abstract

BACKGROUND: Patients experiencing adverse drug events (ADE) in many developing countries are in the best position to report these events to the authorities but need to be empowered to do so. Systematic evaluation of community engagement and patient support especially in rural areas would provide evidence for a program to monitor potential harm from medicines. The aim of this study was to assess the effects of a community dialogue and sensitization (CDS) program on the knowledge, attitude and practises of community members for reporting ADE.

METHODS: This an uncontrolled before-after study was conducted in two eastern Ugandan districts between September 2016 and August 2017.

RESULTS: After implementation of the community dialogue and sensitization (CDS) program, there was an overall 20% (95% CI:16% to 25%) increase in knowledge about ADE in the community compared to before the program began. Awareness levels increased by 50% (95% CI: 37% to 63%) among those with little or no education and by 41% (95% CI: 31% to 52%) among young people (15-24 years). Furthermore, 5% (95% CI: 3% to 7%) more respondents recognized the need for reporting ADEs compared to before the program. Finally, there was a significant increase of 115% (95% CI:137% to 217%) in respondent recognition and reporting of ADEs compared to the beginning of the CDS program. Overall, this community found the CDS program acceptable and proposed aspects that could be improved for future use.

CONCLUSION: Our evaluation showed that the CDS program increased knowledge and improved attitudes by catalyzing discussions among community members and healthcare professionals on health issues and monitoring safety of medicines compared to before the program. Successful implementation of the program depends on holistic health systems strengthening and adaptation to the community's way of life.

Mots-clefs

PRIMMO study protocol: a phase II study combining PD-1 blockade, radiation and immunomodulation to tackle cervical and uterine cancer.

Tuyaerts S, Van Nuffel AMT, Naert E, Van Dam PA, Vuylsteke P, De Caluwé A, Aspeslagh S, Dirix P, Lippens L, De Jaeghere E, Amant F, Vandecasteele K, Denys H.

Références	Doi	IF
BMC Cancer. 2019 May 28;19(1):506	10.1186/s12885-019-5676-3	3,288

Abstract

BACKGROUND: Immunotherapeutic approaches have revolutionized oncological practice but are less evaluated in gynecological malignancies. PD-1/PD-L1 blockade in gynecological cancers showed objective responses in 13-17% of patients. This could be due to immunosuppressive effects exerted by gynecological tumors on the microenvironment and an altered tumor vasculature. In other malignancies, combining checkpoint blockade with radiation delivers benefit that is believed to be due to the abscopal effect. Addition of immune modulation agents has also shown to enhance immune checkpoint blockade efficacy. Therefore we designed a regimen consisting of PD-1 blockade combined with radiation, and different immune/environmental-targeting compounds: repurposed drugs, metronomic chemotherapy and a food supplement. We hypothesize that these will synergistically modulate the tumor microenvironment and induce and sustain an anti-tumor immune response, resulting in tumor regression.

METHODS: PRIMMO is a multi-center, open-label, non-randomized, 3-cohort phase 2 study with safety run-in in patients with recurrent/refractory cervical carcinoma, endometrial carcinoma or uterine sarcoma. Treatment consists of daily intake of vitamin D, lansoprazole, aspirin, cyclophosphamide and curcumin, starting 2 weeks before the first pembrolizumab dose. Pembrolizumab is administered 3-weekly for a total of 6 cycles. Radiation (3 × 8 Gy) is given on days 1, 3 and 5 of the first pembrolizumab dose. The safety run-in consists of 6 patients. In total, 18 and 25 evaluable patients for cervical and endometrial carcinoma respectively are foreseen to enroll. No sample size is determined for uterine sarcoma due to its rarity. The primary objective is objective response rate at week 26 according to immune-related response criteria. Secondary objectives include safety, objective response rate at week 26 according to RECIST v1.1, best overall response, progression-free survival, overall survival and quality of life. Exploratory, translational research aims to evaluate immune biomarkers, extracellular vesicles, cell death biomarkers and the gut microbiome.

DISCUSSION: In this study, a combination of PD-1 blockade, radiation and immune/environmental-targeting compounds is tested, aiming to tackle the tumor microenvironment and induce anti-tumor immunity. Translational research is performed to discover biomarkers related to the mode of action of the combination.

Mots-clefs

Blood platelets; cell-derived microparticles; exosomes; extracellular vesicles; flow cytometry; standardization

Hypertension artérielle : nouvelles recommandations.

Pochet JM, Persu A.

Références

Doi

IF

Louvain Medical 2019;139(5) :274-278

0,02

Abstract

Les nouvelles guidelines de l'ESC/ESH recommandent le recours au monitoring ambulatoire ou à l'auto-mesure pour le diagnostic de l'hypertension et plaident pour un traitement médicamenteux précoce au moyen d'une combinaison fixe associant un bloqueur du système rénine-angiotensine et un antagoniste calcique ou un diurétique thiazide. L'objectif est d'obtenir une pression artérielle de 120-129/70-79 mmHg chez les patients de moins de 65 ans qui le tolèrent. Chez les sujets de plus de 65 ans on visera une pression artérielle de 130-139/70-79 mmHg. La rédaction de guidelines est un peu l'irruption de la politique dans l'evidence-based medicine (EBM) : des experts font le point des données de la littérature et des résultats des essais cliniques publiés pour formuler des recommandations de bonne pratique. L'EBM n'ayant pas réponse à tout, la rédaction de ces guidelines peut donner lieu à des débats vigoureux qui ne sont pas tranchés de la même manière par tous les groupes d'experts. C'est précisément ce qui est arrivé en 2018 avec les guidelines américaines (1) et européennes (2) concernant l'hypertension artérielle.

Mots-clefs

Hypertension ; guidelines

Gammopathie monoclonale de signification indéterminée.

Depaus J.

Références	Doi	IF
Louvain Medical 2019;139(5) :290-292		0,02

Abstract

La gammopathie monoclonale de signification indéterminée (Monoclonal gammopathy of undetermined significance – MGUS dans la terminologie anglo-saxonne) est une anomalie biologique fréquemment retrouvée dans la population générale, en particulier chez le sujet âgé. Il s'agit d'un état prénéoplasique pouvant précéder l'apparition d'un myélome multiple ou d'une hémopathie lymphoïde. Certaines investigations doivent donc être réalisées au diagnostic afin de ne pas méconnaître une hémopathie maligne sous-jacente. Un suivi prolongé sera ensuite assuré. Par ailleurs, même en l'absence d'hémopathies, la MGUS peut être responsable de diverses manifestations cliniques à ne pas méconnaître, d'où le concept nouveau de « Monoclonal Gammopathy of Clinical Significance ». La MGUS peut également s'accompagner d'un risque accru de complications infectieuses, osseuses et thrombo-emboliques.

Mots-clefs

Gammopathie monoclonale de signification indéterminée ; progression ; facteurs de risque

Unexpected findings in the work-up of abdominal pain.

Dupuis F, Dupont M, Postolache A, Schröder E, Seldrum S.

Références

Doi

IF

*Acta Cardiol. 2019 May 25:1-2
[Epub ahead of print]*

10.1080/00015385.2019.1618564

0,607

Abstract

Mots-clefs

Valsalva aneurysm; cardiac extrinsic compression; coarctation of the aorta; congenital rubella syndrome

JUIN

Benchmarking Belgian CRT practice against the rest of Europe: insights from the ESC-CRT survey II.

Gauthey A, Willems R, Vandekerckhove Y, Mullens W, Stefan L, Carryn X, **Blommaert D**, Mairesse G, Dickstein K, Normand C, Linde C, Le Polain de Waroux JB.

<i>Références</i>	<i>Doi</i>	<i>IF</i>
<i>Acta Cardiol. 2019 Jun 13:1-5 [Epub ahead of print]</i>	<i>10.1080/00015385.2019.1621455</i>	<i>0,607</i>

Abstract

This subanalysis of the Euro-CRT survey II specifically focus on Belgian practice for CRT implantation. It explores Belgian adherence with the guidelines but also benchmark CRT practice in Belgium against the other European countries. Overall, Belgian management of CRT implantation is performed with great agreement with guidelines. This report could be used to provide guidance for both practical and economical approaches.

Mots-clefs

CRT survey; cardiac device; guidelines; CRT response; heart failure; resynchronisation therapy

Dosage des D-dimères : variables pré-analytiques, analytiques, post-analytiques et applications cliniques.

Sottiaux JY, Favresse J, Douxfils J, Chatelain B, Jacqmin H, Mullier F.

Références	Doi	IF
Rev Trib Hemostase. 2019 avril-juin [Epub ahead of print]		

Abstract

Les D-dimères comprennent l'ensemble des produits de dégradation de la fibrine stabilisée, induite par la plasmine. Ils peuvent donc être considérés comme un biomarqueur reflétant l'activation de la coagulation et de la fibrinolyse. Le dosage des D-dimères est couramment utilisé pour exclure la maladie thromboembolique veineuse, pour évaluer les risques de récurrence d'une telle affection, et afin de définir la durée optimale d'un traitement anticoagulant. Cette adaptation de l'article original de Favresse et al. 1 est destinée à : (1) faire le point sur la définition des D-dimères ; (2) discuter des variables pré-analytiques affectant la mesure des D-dimères ; (3) examiner et comparer les performances de différents tests et de certaines variables post-analytiques et enfin de (4) discuter de l'utilisation clinique du dosage des D-dimères.

Mots-clefs

produits de dégradation de la fibrine et du fibrinogène ; D-dimère ; pré-analytique ; post-analytique ; analytique ; maladie thromboembolique veineuse

A User-Centered design and usability testing of a web-based medication reconciliation application integrated in an eHealth network.

Marien S, Legrand D, Ramdoyal R, Nsenga J, Ospina G, Ramon V, **Spinewine A**.

Références

Doi

IF

Int J Med Inform. 2019 Jun;126:138-146

10.1016/j.ijmedinf.2019.03.013

3,210

Abstract

BACKGROUND: Medication discrepancies, which are a threat to patient safety, can be reduced by medication reconciliation (MedRec). MedRec is a complex process that can be supported by the use of information technology and patient engagement. Therefore, the SEAMPAT project aims to develop a MedRec IT platform based on two applications. The application for the professionals is called: the «MedRec app».

OBJECTIVE: In the present study, we aimed to describe the development and usability testing of the MedRec app, reporting results of a three iterations user-centered usability evaluation.

METHODS: We used a three phase iterative user-centered study spread over 16 months. At each phase, the usability evaluation included several methods (observations, questionnaires, and follow-up discussions with participants) to collect quantitative and qualitative data in order to improve the current prototype and evolve to the next prototype.

RESULTS: In total, 48 healthcare professionals (25 general practitioners and 23 hospital clinicians) participated to the MedRec app evaluation. There were 14, 32 and 5 participants for phases 1, 2 and 3 respectively. At each phase, many design modifications were done to strengthen usability. Concerning usability, participants considered the prototypes as an acceptable interface with a median System Usability Score of 73 at phase 2 and 75 at phase 3. Participants emphasized the need for improvements concerning workflow integration, usefulness and interoperability.

CONCLUSION: The MedRec app was perceived as being useful, usable and satisfying. However, further improvements are required in several usability aspects. Our study demonstrates the importance of conducting usability assessments before investing time and resources in a large study evaluating the effect of an eMedRec approach on clinical outcomes. Our findings may also increase the chances of acceptability and sustained use over time by clinicians.

Mots-clefs

Continuity of care; Health information technology; Inpatient and outpatient care; Iterative user-centered design; Medication reconciliation; Usability testing; Web-application

Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study.

Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, Béné MC, Broijl A, Caillon H, Caillot D, Corre J, Delforge M, Dejoie T, **Doyen C**, Facon T, Sonntag C, Fontan J, Garderet L, Jie KS, Karlin L, Kuhnowski F, Lambert J, Leleu X, Lenain P, Macro M, Mathiot C, Orsini-Piocelle F, Perrot A, Stoppa AM, van de Donk NW, Wulleme S, Zweegman S, Kolb B, Touzeau C, Roussel M, Tiab M, Marolleau JP, Meuleman N, Vekemans MC, Westerman M, Klein SK, Levin MD, Femand JP, Escoffre-Barbe M, Eveillard JR, Garidi R, Ahmadi T, Zhuang S, Chiu C, Pei L, de Boer C, Smith E, Deraedt W, Kampfenkel T, Schechter J, Vermeulen J, Avet-Loiseau H, Sonneveld P.

Références	Doi	IF
<i>Lancet</i> . 2019 Jul 6;394(10192):29-38	10.1016/S0140-6736(19)31240-1	59,102

Abstract

BACKGROUND: Bortezomib, thalidomide, and dexamethasone (VTd) plus autologous stem-cell transplantation is standard treatment in Europe for transplant-eligible patients with newly diagnosed multiple myeloma. We evaluated whether the addition of daratumumab to VTd before and after autologous stem-cell transplantation would improve stringent complete response rate in patients with newly diagnosed multiple myeloma.

METHODS: In this two-part, randomised, open-label, phase 3 CASSIOPEIA trial, we recruited transplant-eligible patients with newly diagnosed multiple myeloma at 111 European sites. Patients were randomly assigned (1:1) to receive four pre-transplant induction and two post-transplant consolidation cycles of VTd alone (VTd group) or in combination with daratumumab (D-VTd group). The primary endpoint of part 1 was stringent complete response assessed 100 days after transplantation. Part 2 (maintenance) is ongoing. The trial is registered with ClinicalTrials.gov, number NCT02541383.

FINDINGS: Between Sept 22, 2015, and Aug 1, 2017, 1085 patients were enrolled at 111 European sites and were randomly assigned to the D-VTd group (n=543) or the VTd group (n=542). At day 100 after transplantation, 157 (29%) of 543 patients in the D-VTd group and 110 (20%) of 542 patients in the VTd group in the intention-to-treat population had achieved a stringent complete response (odds ratio 1.60, 95% CI 1.21-2.12, p=0.0010). 211 (39%) patients in the D-VTd group versus 141 (26%) in the VTd group achieved a complete response or better, and 346 (64%) of 543 versus 236 (44%) of 542 achieved minimal residual disease-negativity (10⁻⁵ sensitivity threshold, assessed by multiparametric flow cytometry; both p<0.0001). Median progression-free survival from first randomisation was not reached in either group (hazard ratio 0.47, 95% CI 0.33-0.67, p<0.0001). 46 deaths on study were observed (14 vs 32, 0.43, 95% CI 0.23-0.80). The most common grade 3 or 4 adverse events were neutropenia (28% vs 15%), lymphopenia (17% vs 10%), and stomatitis (13% vs 16%).

INTERPRETATION: D-VTd before and after autologous stem-cell transplantation improved depth of response and progression-free survival with acceptable safety. CASSIOPEIA is the first study showing the clinical benefit of daratumumab plus standard of care in transplant-eligible patients with newly diagnosed multiple myeloma.

FUNDING: The Intergroupe Francophone du Myélome and Dutch-Belgian Cooperative Trial Group for Hematology Oncology.

Mots-clefs

Clinical, pathological and molecular factors of aggressiveness in lactotroph tumours.

Trouillas J, **Delgrange E**, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P, Raverot G.

Références

Neuroendocrinology. 2019 Apr 3. [Epub ahead of print]

Doi

10.1159/000499382

IF

3,392

Abstract

The behaviour of lactotroph tumours varies between benign tumours, those cured by treatment, and that of aggressive tumours, and carcinomas with metastasis. Identification of clinical, pathological and molecular factors is essential for the early identification of patients that may have such aggressive tumours. Plasma prolactin levels and tumour size and invasion, per se, are not prognostic factors. However, tumours appearing at a young age (<20 years), especially in boys, and the presence of genetic predisposition have a poorer prognosis. In addition, lactotroph tumours in men differ from those in women, being larger, more often invasive, and resistant to dopamine agonists. They are also more often high-grade with a high risk of recurrence and malignancy. The expression of estrogen receptor is lower than in women and is closely correlated to aggressiveness. Proliferation markers (Ki-67 expression: $\geq 3\%$, mitotic count $n > 2$) are correlated to invasion and proliferation, but, taken alone, their prognostic value is debatable. Based on a 5-tiered clinicopathological classification, and taking into account invasion and proliferation, a grade 2b (aggressive) lactotroph tumour has a 20× risk of progression compared to a grade 1a (benign) tumour. Moreover, lactotroph tumours are the second-most frequent aggressive and malignant tumour. Other factors, such as the expression of growth factors (vascular endothelial growth factor [VEGF] and epidermal growth factor [EGF]), the genes regulating invasion, differentiation and proliferation, adhesion molecules (E-cadherin), matrix metalloproteinase 9, and chromosome abnormalities (chromosomes 11, 19, and 1), have also been correlated with aggressiveness. Currently, clinical signs, a prognostic classification, and molecular and genetic markers may all help the clinician in the early identification of aggressive lactotroph tumours and enable stratification of their management.

Mots-clefs

Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients: final results of the IFM 2014-04 (Etoile du Nord) trial.

Boyle EM, Leleu X, Petillon MO, Karlin L, **Doyen C**, Demarquette H, Royer B, Macro M, Moreau P, Fostier K, Marie-Lorraine C, Zarnitsky C, Perrot A, Herbaux C, Poulain S, Manier S, Beauvais D, Walker BA, Wardell CP, Vincent L, Frenzel L, Caillon H, Susanna S, Dejoie T, Avet-Loiseau H, Mohty M, Facon T; IFM2014-04 investigators.

Références	Doi	IF
<i>Br J Haematol.</i> 2019 Jun 19 [Epub ahead of print]	10.1111/bjh.16059	5,67

Abstract

Single agent daratumumab has shown clinical activity in relapsed, refractory multiple myeloma (RRMM). The Intergroupe Francophone du Myélome 2014-04 trial was designed to further investigate daratumumab in combination with dexamethasone in triple RRMM patients. Patients received daratumumab infusions in combination with weekly dexamethasone until disease progression or unacceptable toxicity. Fifty-seven patients were included in the trial and evaluable for response. The overall response rate and the clinical benefit rate were 33% (n = 19) and 48% (n = 27), respectively. Five (8.8%) patients achieved a very good partial response or better. The median time to response was 4 weeks. For responding patients, the median progression-free survival was 6.6 months, compared to 3.7 months (3.0-5.5) for those with a minimal or stable disease. The median overall survival (OS) for all patients was 16.7 months (11.2-24.0). For responding patients, the median OS was 23.23 months, whereas that of patients with progressive disease was 2.97 months. The incidence of infusion-related reactions was 37%; all cases were manageable and did not lead to dose reduction or permanent treatment discontinuation. These data demonstrate that treatment with daratumumab and dexamethasone results in a meaningful long-term benefit with an acceptable safety profile for patients with triple RRMM.

Mots-clefs

clinical trial; daratumumab; myeloma therapy

Hyaluronan derivative HYMOVIS® increases cartilage volume and type ii collagen turnover in osteoarthritic knee: data from MOKHA study.

Henrotin Y, Bannuru R, Malaise M, Ea HK, Confavreux C, Bentin J, Urbin-Choffray D, Conrozier T, **Brasseur JP**, Thomas P, Hick AC, Marinello A, Giordan N, Richette P.

Références	Doi	IF
<i>BMC Musculoskelet Disord.</i> 2019 Jun 18;20(1):293	10.1186/s12891-019-2667-0	2,002

Abstract

BACKGROUND: The objective of this pilot study was to identify biological, clinical or structural biomarkers of an intra-articular hyaluronic acid injection efficacy (HYMOVIS®) for the design of a larger placebo-controlled clinical trial studying the disease-modifying activity of this treatment.

METHODS: Forty six patients with symptomatic knee Osteoarthritis (OA) were enrolled in this open-label, prospective, multicenter, pilot study. Patients received two treatment cycles of intra-articular injections (3 mL) of HYMOVIS® (8 mg/mL of hyaluronic acid hexadecylamide) at 6 months interval. Each treatment cycle involved two intra-articular injections 1 week apart. All patients had Magnetic Resonance Imaging (MRI) of the target knee at baseline and 1 year, and blood samples to assess joint biomarkers. The primary outcome was the change in type II collagen-specific biomarkers (Coll2-1, Coll2-1NO₂ and CTX-II) after HYMOVIS® treatment versus baseline. Secondary endpoints included levels changes in aggrecan chondroitin sulfate 846 epitope (CS-846), Cartilage Oligomeric Matrix Protein (COMP), procollagen type II N-terminal propeptide (PIIANP), Matrix Metalloprotease (MMP)-3, Myeloperoxidase (MPO) and Interleukin (IL)-6 serum biomarkers, the ratio Coll2-1/PIIANP, CTX-II/PIIANP, variation of MRI cartilage volume, and Knee injury and Osteoarthritis Outcome Score (KOOS) index.

RESULTS: Coll2-1 serum levels significantly increased overtime while Coll2-1NO₂ levels were only increased at D360. Serum PIIANP levels also progressively and significantly enhanced with time. In contrast, other serum biomarker levels including CTX-II, CS-846, COMP, MMP-3, MPO or IL-6 did not change significantly overtime. Interestingly, the ratios Coll2-1/PIIANP and CTX-II/PIIANP decreased, indicating a decrease of cartilage catabolism. Compared to baseline value, MRI cartilage volume and thickness increased in lateral femoral and lateral trochlea compartments and not in medial compartment. These results, in addition to an improvement of T2 mapping score suggest a positive structural effect of the product. Interestingly, WOMBS effusion score, an indicator of synovitis, significantly decreased. Finally, global KOOS score and subscales significantly increased overtime while pain at rest, walking pain and patients or investigators global assessment of disease activity decreased. The safety profile was favorable with a low incidence of injection-site pain.

CONCLUSION: HYMOVIS®, a well-tolerated intra-articular treatment, significantly enhanced type II collagen turnover as suggested by the increase in Coll2-1 and PIIANP levels and cartilage volume observed by MRI in lateral knee compartment. Importantly, this study provides critical information for the design of a larger phase III clinical trial investigating Disease Modifying effect of HYMOVIS®.

Mots-clefs

Biomarkers; Cartilage; Hyaluronic acid; Osteoarthritis ventilation

Long term outcome after 48 Gy stereotactic ablative body radiotherapy for peripheral stage I non-small cell lung cancer.

Dubaere E, Goffaux M, Wanet M, Bihin B, Gheldof C, Demoulin AS, Bolly A, Bustin F, Duplaquet F, Baugnee PE, Gustin M, Hers V, Maisin F, Marchand E, Ocak S, Pirard L, Van-cutsem O, Van Neck E, Vandermoten G, Zaharia L, Remouchamps V.

Références	Doi	IF
BMC Cancer. 2019 Jun 28;19(1):639	10.1186/s12885-019-5863-2	3,288

Abstract

BACKGROUND: To evaluate the outcome of patients treated with stereotactic ablative body radiotherapy (SABR) with curative intent for stage I non-small cell lung cancer (NSCLC) with regard to local, regional and distant tumor control, disease-free survival (DFS), overall survival (OS) and toxicity.

METHODS: Data of 300 patients treated with SABR for NSCLC cancer for the period of November 2007 to June 2016 were retrospectively analyzed. Of which, 189 patients had single primary lung lesion and were included in the study. The prescribed dose for the tumor was 48 Gy, given in 12 Gy × 4 fractions for all patients. In 2010, an improved protocol was established in advanced technology for the planning CT, dose calculation and imaging. Cumulative incidence function (CIF) of local, regional, distant or any recurrences were computed using competing risk analysis with death as a competing event. Survivals (DFS and OS) were estimated using the Kaplan-Meier method and Cox proportional regression was used for comparisons. Toxicities were graded according to the common terminology criteria for adverse events version 4.0 (CTCAE v.4).

RESULTS: Diagnosis was histologically confirmed in 42% of the patients (N = 80). At 1, 2 and 4 years, the cumulative incidence function (CIF) of local relapses were 8% [4-13%], 15% [10-21%] and 18% [12-25%], the CIF of regional relapses were 4% [2-8%], 10% [6-16%] and 12% [8-19%], the CIF of distant relapses were 9% [5-14%], 15% [11-22%] and 20% [15-28%] and the CIF of any relapses were 14% [10-20%], 28% [22-36%], 34% [27-43%], respectively. After 1, 2 and 4 years, the OS rates were 83% [95% CI: 78-89%] (N = 128), 65% [95% CI: 57-73%] (N = 78) and 37% [95% CI: 29-47%] (N = 53), respectively. The median survival time was 37 months. The DFS after 1, 2 and 4 years reached 75% [95% CI: 68-81%] (N = 114), 49% [95% CI: 42-58%] (N = 60) and 31% [95% CI: 24-41%] (N = 41), respectively. No grade 4 or 5 toxicity was observed.

CONCLUSIONS: We observed a long-term local control and survival after SABR for peripheral stage I NSCLC in this large series of patients with the expected low toxicity.

Mots-clefs

Lung cancer; Non-small cell lung cancer; Stereotactic ablative radiotherapy; Survival

Rationale and design of OPTimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial.

Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K, Schwab N, Hossmann S, Schneider C, Jegerlehner S, Floriani C, Limacher A, Jungo KT, Huibers CJA, Streit S, Schwenkglens M, Spruit M, Van Dorland A, Donzé J, Kearney PM8, Jüni P, Aujesky D, Jansen P, Boland B, Dalleur O, Byrne S, Knol W, **Spinewine A**, O'Mahony D, Trelle S, Rodondi N.

Références	Doi	IF
BMJ Open. 2019 Jun 3;9(6):e026769	10.1136/bmjopen-2018-026769	2,376

Abstract

INTRODUCTION: Multimorbidity and polypharmacy are important risk factors for drug-related hospital admissions (DRAs). DRAs are often linked to prescribing problems (overprescribing and underprescribing), as well as non-adherence with drug regimens for different reasons. In this trial, we aim to assess whether a structured medication review compared with standard care can reduce DRAs in multimorbid older patients with polypharmacy.

METHODS AND ANALYSIS: OPTimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people is a European multicentre, cluster randomised, controlled trial. Hospitalised patients ≥ 70 years with ≥ 3 chronic medical conditions and concurrent use of ≥ 5 chronic medications are included in the four participating study centres of Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium) and Cork (Ireland). Patients treated by the same prescribing physician constitute a cluster, and clusters are randomised 1:1 to either standard care or Systematic Tool to Reduce Inappropriate Prescribing (STRIP) intervention with the help of a clinical decision support system, the STRIP Assistant. STRIP is a structured method performing customised medication reviews, based on Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment criteria to detect potentially inappropriate prescribing. The primary endpoint is any DRA where the main reason or a contributory reason for the patient's admission is caused by overtreatment or undertreatment, and/or inappropriate treatment. Secondary endpoints include number of any hospitalisations, all-cause mortality, number of falls, quality of life, degree of polypharmacy, activities of daily living, patient's drug compliance, the number of significant drug-drug interactions, drug overuse and underuse and potentially inappropriate medication.

ETHICS AND DISSEMINATION: The local Ethics Committees in Switzerland, Ireland, The Netherlands and Belgium approved this trial protocol. We will publish the results of this trial in a peer-reviewed journal.

MAIN FUNDING: European Union's Horizon 2020 programme.

Mots-clefs

clinical pharmacology; general medicine (see internal medicine); geriatric medicine; internal medicine

Long-term stability of an infusion containing paracetamol, alizapride, ketorolac and tramadol in glass bottles at $5 \pm 3^\circ\text{C}$

Colsoul ML, Hecq JD, Soumoy L, Charles O, Goderniaux N, Bihin B, Jamart J, Galanti L.

Références

Doi

IF

Eur J Hosp Pharm 2019 Jun [Epub ahead of print]

10.1136/ejhpharm-2019-001966

0,717

Abstract

BACKGROUND AND OBJECTIVE: Infusion containing paracetamol, alizapride, ketorolac and tramadol is used after a general anaesthesia in order to limit pain, fever and nausea. Currently, these infusions are prepared according to demand in the anaesthesia unit, but the preparation in advance could improve quality of preparation and time management. The aim of this study was to investigate the long-term stability of this infusion in glass bottles at $5^\circ\text{C} \pm 3^\circ\text{C}$.

METHOD: Five bottles of infusion were stored at $5^\circ\text{C} \pm 3^\circ\text{C}$ for 60 days. A visual and microscope inspection were performed periodically to observe any particle appearance or colour change. pH and absorbance at three wavelengths were measured. The concentrations were measured by ultra-high performance liquid chromatography – diode array detection.

RESULTS: Multiple verifications were performed during the first 35 days and no crystal, impurity or colour change were observed. At the next time point (42nd day), crystals were visible to the naked eye. pH and absorbance at 350 nm and 550 nm were stable. A slight increase in the absorbance at 410 nm was observed during the study, suggesting that a degradation product could be formed and absorb at this wavelength. The infusion was considered chemically stable while the lower one-sided prediction limit at 95% remains superior to 90% of the initial concentration. Concentration measurements demonstrated that ketorolac and alizapride remained stable in the infusion for 35 days. The stability of tramadol was 28 days. However, degradation of paracetamol was much faster given that concentration has fallen below 90% of the initial concentration after 7 days.

CONCLUSION: Infusion of paracetamol, alizapride, ketorolac and tramadol remains stable for 7 days in glass bottles at $5^\circ\text{C} \pm 3^\circ\text{C}$ and could be prepared in advance with these storage conditions.

Mots-clefs

General Pharmacology ; Toxicology and Pharmaceutics

Centralisation des injectables et accréditations des hôpitaux

Hecq JD.

Références	Doi	IF
J PHarm Bel, 2019;101(2) :38-39		0,04

Abstract

La stabilité physico-chimique d'une préparation injectable (IV) est conditionnée par différents paramètres. Une collaboration entre pharmacie, laboratoire de chimie et statisticiens de l'unité de support scientifique s'est installée en 1996, afin de réaliser des études de stabilité chimique à long terme d'IV couramment utilisés et de pouvoir prendre en charge leur préparation en pharmacie.

Mots-clefs

100 ans de Sciences et Pratiques Pharmaceutiques

Hecq JD.

Références

Doi

IF

J PHarm Bel, 2019;101(2):36

0,04

Abstract

Mots-clefs

Les mouvements de la mandibule informent sur l'effet thérapeutique de l'orthèse d'avancée mandibulaire

Martinot JB, Crespeigne E, Bolly A, Butenda Babapu D, Le-Dong NN.

Références

Doi

IF

VCP 2019;24(2):46-50

Abstract

L'étude des mouvements mandibulaires pendant le sommeil informent de manière précise sur l'évolution des indices d'apnées/hypopnées au cours de la titration de l'orthèse d'avancée mandibulaire dans le traitement du syndrome des apnées obstructives. Ces mouvements mandibulaires peuvent, maintenant, être monitorés nuit après nuit par une nouvelle technologie connectée, qui vérifie la levée de l'effort respiratoire sous l'effet de l'orthèse en avancée.

Mots-clefs

Serotonin; UHPLC-MS/MS; platelet; thromboxane B2; triple quadrupole

Head and Body positions as risk-factors for sleep obstructive breathing

Martinot JB, Le-Dong NN, Cuthbert V, Denison S, Tamisier R, Pepin JL.

Références

Doi

IF

ERJ Open Research 2019;5(supp3):116

10.1193/23120541

1,135

Abstract

OBJECTIVE: We explored the causal relationship between Head-Body positions (HBp) and Sleep obstructive apnea/hypopnea (OAH) to fill the evidence gap in this topic.

METHODS: Rotations (pitch/yaw) and directions (prone, supine, up/left, supine, right) of HBp were captured by two miniaturized sensors under 45° segments during type1 PSG in 20 consecutive OSA patients. Sequential categorical data of Arousals (A, n=559) and OAH events (n=630) (accordingly to AASM2012) associated with HBp status (n=1633) were built. A timestamps-based algorithm was applied to extract every possible combinations between changes in HBp and events. The association between HBp and events risk was evaluated with Lasso-logic and RandomForest models

RESULTS: Head and body prone pitching (PP) and right yawing (RY) were found significantly associated to either A or OAH events. Head position played the most important role (OR=2.2 for PP and 3.9 for RY), compared to that of body postural changes (OR=1.2 for RY and OR=1.1 for PP). Chronological order analysis showed that HBp changes occurred after A (73.7%) or OAH (72.6%) episodes. A and OAH events were triggered by HBp in only 23% observations. Rarely, A and OAH events occurred during a long and stable HBp (2.5%).

CONCLUSION: Prone pitching and right yawing were the most important positions contributing to the classification of A and OAH events. HBp seemed here more likely consequences than causes of A or OAH risk.

Mots-clefs

Comment on: 'Resolution of CMV Infection in the Bowel on Vedolizumab Therapy'.

Hommel C, Pillet S, Rahier JF.

Références

J Crohns Colitis. 2019 Jun 4. pii: jjz108 [Epub ahead of print]

Doi

10.2147/COPD.S164259

IF

7,827

Abstract

Mots-clefs

Cytomegalovirus; Ulcerative Colitis; Vedolizumab; qPCR

Learning a Bimanual Cooperative Skill in Chronic Stroke Under Noninvasive Brain Stimulation: A Randomized Controlled Trial.

Doost MY, Orban de Xivry JJ, Herman B, Vanthournhout L, Riga A, Bihin B, Jamart J, Laloux P, Raymackers JM, Vandermeeren Y.

Références

Neurorehabil Neural Repair. 2019 Jun;33(6):486-498

Doi

10.1177/1545968319847963

IF

4,711

Abstract

BACKGROUND: Transcranial direct current stimulation (tDCS) has been suggested to improve poststroke recovery. However, its effects on bimanual motor learning after stroke have not previously been explored. Objective. We investigated whether dual-tDCS of the primary motor cortex (M1), with cathodal and anodal tDCS applied over undamaged and damaged hemispheres, respectively, improves learning and retention of a new bimanual cooperative motor skill in stroke patients.

METHOD: Twenty-one chronic hemiparetic patients were recruited for a randomized, double-blinded, cross-over, sham-controlled trial. While receiving real or sham dual-tDCS, they trained on a bimanual cooperative task called CIRCUIT. Changes in performance were quantified via bimanual speed/accuracy trade-off (Bi-SAT) and bimanual coordination factor (Bi-Co) before, during, and 0, 30, and 60 minutes after dual-tDCS, as well as one week later to measure retention. A generalization test then followed, where patients were asked to complete a new CIRCUIT layout.

RESULTS: The patients were able to learn and retain the bimanual cooperative skill. However, a general linear mixed model did not detect a significant difference in retention between the real and sham dual-tDCS conditions for either Bi-SAT or Bi-Co. Similarly, no difference in generalization was detected for Bi-SAT or Bi-Co.

CONCLUSION: The chronic hemiparetic stroke patients learned and retained the complex bimanual cooperative task and generalized the newly acquired skills to other tasks, indicating that bimanual CIRCUIT training is promising as a neurorehabilitation approach. However, bimanual motor skill learning was not enhanced by dual-tDCS in these patients.

Mots-clefs

bimanual coordination; motor skill learning; neurorehabilitation; noninvasive brain stimulation; stroke; tDCS

JUILLET

Clinical and biological features of PTPN2-deleted adult and pediatric T-cell acute lymphoblastic leukemia.

Alcantara M, Simonin M, Lhermitte L, Touzart A, Dourthe ME, Latiri M, Grardel N, Cayuela JM, Chalandon Y, **Graux C**, Dombret H, Ifrah N, Petit A, Macintyre E, Baruchel A, Boissel N, Asnafi V.

Références	Doi	IF
Blood Adv. 2019 Jul 9;3(13):1981-1988	10.1182/bloodadvances.2018028993	

Abstract

Protein tyrosine phosphatase nonreceptor type 2 (PTPN2) is a phosphatase known to be a tumor suppressor gene in T-cell acute lymphoblastic leukemia (T-ALL). Because the full clinicobiologic characteristics of PTPN2 loss remain poorly reported, we aimed to provide a comprehensive analysis of PTPN2 deletions within a cohort of 430 patients, including 216 adults and 214 children treated according to the GRAAL03/05 (#NCT00222027 and #NCT00327678) and the FRALLE2000 protocols, respectively. We used multiplex ligation-dependent probe amplification to identify an 8% incidence of PTPN2 deletion, which was comparable in adult (9%) and pediatric (6%) populations. PTPN2 deletions were significantly associated with an $\alpha\beta$ lineage and TLX1 deregulation. Analysis of the mutational genotype of adult T-ALL revealed a positive correlation between PTPN2 deletions and gain-of-function alterations in the IL7R/JAK-STAT signaling pathway as well as PHF6 and WT1 mutations. Of note, PTPN2 and PTEN (phosphatase and tensin homolog) deletions were mutually exclusive. Regarding treatment response, PTPN2-deleted T-ALLs were associated with a higher glucocorticoid response and a trend for improved survival in children, but not in adults, with a 5-year cumulative incidence of relapse of 8% for PTPN2-deleted pediatric cases vs 26% ($P = .177$).

Mots-clefs

Communication; Healthcare professionals; Interaction analysis system; Patient outcome; Patient-centeredness; Uncertainty

Chromothripsis in an Early Recurrent Chordoid Meningioma.

Baltus C, Toffoli S, London F, Delrée P, Gilliard C, Gustin T.

Références	Doi	IF
World Neurosurg. 2019 Jul 9;130:380-385 [Epub ahead of print]	10.1016/j.wneu.2019.07.003	1,723

Abstract

BACKGROUND: Chromothripsis is characterized by a multitude of chromosomal rearrangements during a unique cataclysmic event in a cell life. Disintegration of one or several chromosomes is followed by a chaotic rearrangement of generated fragments. It might play a role in oncogenesis and tumor progression. It is observed in 2%-3% of cancers and is rarely reported in benign tumors. We report a case of massive chromothripsis in a fast growing chordoid meningioma.

CASE DESCRIPTION: A 55-year-old woman was admitted for a meningeal mass developing in the right parietal parasagittal area. She underwent subtotal resection of the tumor. Histologic analysis revealed a chordoid meningioma (World Health Organization grade II). Six months later, magnetic resonance imaging showed a large bilateral tumor recurrence. After a second surgery, the patient received radiotherapy. Thereafter, the clinical course was uneventful. Comparative genomic hybridization showed only a monosomy X in the primary tumor. In the recurrent meningioma, this anomaly was associated with a massive chromothripsis including more than 370 chromosomal abnormalities affecting chromosomes 1-22.

CONCLUSIONS: Chromothripsis is rarely described in benign tumors and especially in meningiomas. In the presented case, the high number of chromosomal rearrangements and the onset of this phenomenon at a later stage of tumor progression are very unusual. The role of surgical stress on the emergence of chromothripsis and its relation with tumor aggressiveness are discussed.

Mots-clefs

Chordoid meningioma; Chromothripsis; Recurrence

Prospective and comparative study of paroxysmal nocturnal hemoglobinuria patients treated or not by eculizumab: Focus on platelet extracellular vesicles.

Devalet B, Wannez A, Bailly N, Alpan L, Gheldof D, Douxfils J, Bihin B, Chatelain B, Dogné JM, Chatelain C, Mullier F.

Références

Medicine (Baltimore). 2019 Jul;98(27):e16164

Doi

10.1097/MD.00000000000016164

IF

2,133

Abstract

Thrombosis are severe complications of paroxysmal nocturnal hemoglobinuria (PNH), effectively reduced by eculizumab. Extracellular vesicles (EVs) may play a central role. The objective of this study was to assess the procoagulant activity of plasma isolated from PNH patients (treated or not by eculizumab) and to quantify their circulating EVs. We iteratively collected the platelet-free-plasma of 17 PNH patients and 16 matched healthy volunteers, quantified their circulating EVs by flow cytometry and evaluated their procoagulant activity by thrombin generation and STA-Procoag-procoagulant phospholipid (PPL) assays. A significant decrease of EVs from platelets ($P=.024$) and an increase of the STA-Procoag-PPL clotting time ($P=.049$) was observed after initiation of eculizumab and up to 11 weeks after. This reduction of prothrombotic biomarkers was not observed with the thrombin generation test due to a lack of sensitivity of this assay. Active hemolysis was observed in 90% of patients and elevated D-dimers in 41% of them. However, no significant difference was observed between patients and control subjects regarding the procoagulant activity, the EVs quantity, or the cellular origin. Lactate dehydrogenase (LDH) levels were lower in eculizumab-treated patients compared to nontreated patients (441 vs 2448 IU/L). D-dimers and LDH decreased after administration of eculizumab (mean decrease of 1307 ng/mL and 4159 IU/L, respectively). These observations suggest a decrease of the phospholipid-dependent procoagulant potential of EVs after eculizumab therapy in PNH patients. TRIAL REGISTRATION:: NUB: B039201214365

Mots-clefs

Chordoid meningioma; Chromothripsis; Recurrence

Standardization of Flow Cytometric Immunophenotyping for Hematological Malignancies: The FranceFlow Group Experience.

Solly F, Angelot-Delettre F, Ticchioni M, Geneviève F, Rambaud H, Baseggio L, Plesa A, Debliquis A, Garnache-Ottou F, Roggy A, Campos L, Aanei C, Rosenthal-Allieri A, Georget MT, Lachot S, Jacob MC, Robillard N, Wulleme S, Andre-Kerneis E, Cornet E, Salaun V, Bennami H, Lhoumeau AC, Arnoulet C, **Jacqmin H, Neyman N**, Latger-Cannard V, Massin F, Lainey E, Le Garff-Tavernier M, Costopoulos M, Roussel M, Mayeur-Rousse C, Eischen A, Raggeneau V, Derrieux C, Maurer M, Asnafi V, Trinquand A, Brouzes C, Lhermitte L

<i>Références</i>	<i>Doi</i>	<i>IF</i>
<i>Cytometry A. 2019 Jul 31 [Epub ahead of print]</i>	<i>10.1002/cyto.a.23844</i>	<i>3,433</i>

Abstract

Flow cytometry is broadly used for the identification, characterization, and monitoring of hematological malignancies. However, the use of clinical flow cytometry is restricted by its lack of reproducibility across multiple centers. Since 2006, the EuroFlow consortium has been developing a standardized procedure detailing the whole process from instrument settings to data analysis. The FranceFlow group was created in 2010 with the intention to educate participating centers in France about the standardized instrument setting protocol (SOP) developed by the EuroFlow consortium and to organise several rounds of quality controls (QCs) in order to evaluate the feasibility of its application and its results. Here, we report the 5 year experience of the FranceFlow group and the results of the seven QCs of 23 instruments, involving up to 19 centers, in France and in Belgium. The FranceFlow group demonstrates that both the distribution and applicability of the SOP have been successful. Intercenter reproducibility was evaluated using both normal and pathological blood samples. Coefficients of variation (CVs) across the centers were <7% for the percentages of cell subsets and <30% for the median fluorescence intensities (MFIs) of the markers tested. Intracenter reproducibility provided similar results with CVs of <3% for the percentages of the majority of cell subsets, and CVs of <20% for the MFI values for the majority of markers. Altogether, the FranceFlow group show that the 19 participating labs might be considered as one unique laboratory with 23 identical flow cytometers able to reproduce identical results. Therefore, SOP significantly improves reproducibility of clinical flow in hematology and opens new avenues by providing a robust companion diagnostic tool for clinical trials in hematology.

Mots-clefs

FranceFlow; flow cytometry; hematology; immunophenotyping; instrument settings; quality controls; standardization

Physical instability of an infusion containing ropivacaine, clonidine and adrenaline tartrate in syringes for pre-operative administration.

Colsoul ML, Lardinois B, Galanti L, Soumoy L, Hecq JD.

Références

Doi

IF

Anaesth Crit Care Pain Med. 2019 Jul 18. pii: S2352-5568(19)30224-3 [Epub ahead of print]

10.1016/j.accpm.2019.07.006

2,734

Abstract

Mots-clefs

Bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: a double-blind multicenter randomized placebo controlled three-arm study.

Henrotin Y, Malaise M, Wittoek R, de Vlam K, **Brasseur JP**, Luyten FP, Jiangang Q, Van den Berghe M, Uhoda R, Bentin J, De Vroey T, Erpicum L, Donneau AF, Dierckxsens Y.

Références	Doi	IF
Arthritis Res Ther. 2019 Jul 27;21(1):179	10.1186/s13075-019-1960-5	4,269

Abstract

OBJECTIVES: Comparison of two doses of bio-optimized Curcuma longa extract (BCL) in the management of symptomatic knee osteoarthritis (OA).

METHODS: A prospective, randomized, 3-month, double-blind, multicenter, three-group, placebo-controlled trial assessing Patient Global Assessment of Disease Activity (PGADA) and serum sColl2-1, a biomarker of cartilage degradation, as co-primary endpoints. Pain on visual analog scale (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), and paracetamol/non-steroidal anti-inflammatory drug (NSAID) consumption were used as secondary endpoints.

RESULTS: One hundred fifty patients with knee OA were followed for 90 days. Low and high doses of BCL showed a greater decrease of PGADA than placebo. Analysis of sColl2-1 showed in the placebo and BCL low-dose groups, but not in the BCL high-dose group, a transient but non-significant increase of sColl2-1 between T₀ and T₁. Thereafter, in all groups, sColl2-1 decreased between T₁ and T₃ (all $p < 0.01$), but no difference between the groups was found. Pain reduction at day 90 in the low- and high-dose BCL groups (-29.5 mm and -36.5 mm) was higher than that in the placebo (-8 mm; $p = 0.018$). The global KOOS significantly decreased overtime, but changes were comparable across treatment arms. The ratio of patients with adverse events (AE) related to the product was similar in the placebo and treatment groups, but the number of AE linked to the product was higher in the high-dose BCL group compared to the placebo ($p = 0.012$).

CONCLUSIONS: BCL appeared safe and well-tolerated with no evidence of severe adverse effects. Efficacy analysis suggested positive trends for measurements of PGADA and serum levels of an OA biomarker and showed a rapid and significant decrease of pain in knee OA (Trial registration: ISRCTN, ISRCTN12345678. Registered 21 September 2016-retrospectively registered,

Mots-clefs

Biomarkers; Curcumin; Osteoarthritis

Automated Compounding of Intravenous Therapy in European Countries: A Review in 2019.

Soumoy L, Hecq JD

Références	Doi	IF
Pharm Technol Hosp Pharm, 2019;4(2):51-57	10.1515/pthp-2019-0008	0,35

Abstract

Automated compounding systems appeared on the market during these last 15 years as an alternative for manual compounding of intravenous (IVD) drugs. A literature review was conducted on reconstitution of IVD. The following methods were identified: manual, semi-automatic and automatic. A classification was carried out in three categories: automatic syringes, peristaltic pumps, and compounding doses robots. The number of compounding robots is increasing. A table describes the different features of each device. The ampuls cannot be supported by these robots. Large doses vials improve the time of reconstitution compared to current dosage vials. Advantages of automated preparation are: higher consistency of process and products, higher accuracy of products, Integrated digitized processing, precise, complete documentation, reduced effort and wrist injuries, reduced personnel requirement, increased worker satisfaction. Disadvantages of automated preparation are: risk of failure/down time, dependency on power supply, software (updates), high investment costs/high maintenance costs, specialized personnel with additional training, decreased worker satisfaction (early adopter), complexity when products are switched or added, potential for new errors. This review allows the potential user to know the current availability on the market.

Mots-clefs

AOÛT

Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma.

Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, Moreau P, Dingli D, Cole C, Lonial S, Dimopoulos M, Stewart AK, Richter J, Vij R, Tuchman S, Raab MS, Weisel KC, Delforge M, Cornell RF, Kaminetzky D, Hoffman JE, Costa LJ, Parker TL, Levy M, Schreder M, Meuleman N, Frenzel L, Mohty M, Choquet S, Schiller G, Comenzo RL, Engelhardt M, Illmer T, Vlummens P, **Doyen C**, Facon T, Karlin L, Perrot A, Podar K, Kauffman MG, Shacham S, Li L, Tang S, Picklesimer C, Saint-Martin JR, Crochiere M, Chang H, Parekh S, Landesman Y, Shah J, Richardson PG, Jagannath S.

Références	Doi	IF
<i>N Engl J Med.</i> 2019 Aug 22;381(8):727-738	10.1056/NEJMoa1903455	70,670

Abstract

BACKGROUND: Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumor suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation, is a potential novel treatment for myeloma that is refractory to current therapeutic options.

METHODS: We administered oral selinexor (80 mg) plus dexamethasone (20 mg) twice weekly to patients with myeloma who had previous exposure to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab (triple-class refractory). The primary end point was overall response, defined as a partial response or better, with response assessed by an independent review committee. Clinical benefit, defined as a minimal response or better, was a secondary end point.

RESULTS: A total of 122 patients in the United States and Europe were included in the modified intention-to-treat population (primary analysis), and 123 were included in the safety population. The median age was 65 years, and the median number of previous regimens was 7; a total of 53% of the patients had high-risk cytogenetic abnormalities. A partial response or better was observed in 26% of patients (95% confidence interval, 19 to 35), including two stringent complete responses; 39% of patients had a minimal response or better. The median duration of response was 4.4 months, median progression-free survival was 3.7 months, and median overall survival was 8.6 months. Fatigue, nausea, and decreased appetite were common and were typically grade 1 or 2 (grade 3 events were noted in up to 25% of patients, and no grade 4 events were reported). Thrombocytopenia occurred in 73% of the patients (grade 3 in 25% and grade 4 in 33%). Thrombocytopenia led to bleeding events of grade 3 or higher in 6 patients.

CONCLUSIONS: Selinexor-dexamethasone resulted in objective treatment responses in patients with myeloma refractory to currently available therapies. (Funded by Karyopharm Therapeutics; STORM ClinicalTrials.gov number, NCT02336815.).

Mots-clefs

Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes Study.

Strauven G, Anrys P, Vandael E, Henrard S, De Lepeleire J, **Spinewine A, Foulon V.**

Références	Doi	IF
<i>J Am Med Dir Assoc.</i> 2019 Aug 8. pii: S1525-8610(19)30492-X [Epub ahead of print]	10.1016/j.jamda.2019.06.006	4,899

Abstract

OBJECTIVES: To investigate the impact of a complex multifaceted intervention on the appropriateness of prescribing for Belgian nursing home (NH) residents.

DESIGN: A multicenter, nonblinded, cluster-randomized controlled trial, with randomization at the NH level, was set up [Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes (COME-ON) Study]. The complex intervention consisted of repeated interdisciplinary case conferences (ICCs) involving the general practitioner, pharmacist, and nurse, aimed at performing a medication review for each NH resident included. The ICCs were supported by a blended training program and local interdisciplinary meetings (discussion of the appropriate use of specific medication classes at the NH level). Control NHs delivered usual care. (isrctn.com: ISRCTN66138978).

SETTING AND PARTICIPANTS: Belgian NHs with at least 35 NH residents were eligible to participate. Eligible residents were those aged 65 years or over, not receiving palliative care, and being treated by a participating general practitioner.

MEASURES: The primary outcome measure related to appropriateness of prescribing at resident level and was considered successful when at least 1 potentially inappropriate medication (PIM) or potential prescribing omission (PPO) present at baseline had been solved at the end of study and when there were no new PIMs or PPOs at the end of study compared with baseline. Secondary outcomes included clinical outcomes, medication use, criterion-specific prevalence of PIMs and PPOs, and ICC outcomes.

RESULTS: In total, 54 NHs (24 intervention; 30 control) and 1804 NH residents (847 intervention; 957 control) participated. Using a 3-level mixed-effects model accounting for data clustering, a significant effect in favor of the intervention was observed (odds ratio 1.479 [95% confidence interval 1.062-2.059, $P = .021$]). There was no significant difference between groups for most clinical outcomes. The median number of medications did not change over time in either group.

CONCLUSIONS AND IMPLICATIONS: The complex multifaceted intervention tested in the COME-ON study successfully improved appropriateness of prescribing in NHs.

Mots-clefs

Nursing homes; appropriateness of prescribing; complex intervention; interdisciplinary collaboration; medication review

Long-term Physicochemical Stability of Concentrated Solutions of Sodium Valproate in Polypropylene Syringes for Administration in the Intensive Care Unit.

Lardinois B, Baltzis A, Braibant M, Soumoy L, Jamart J, Bihin B, Hecq JD, Galanti L.

Références

Doi

IF

Int J Pharm Compd. 2019 Jul-Aug;23(4):320-323.

0,118

Abstract

In some situations, drug solutions in higher concentrations are used in intensive care units. The objective of this study was to evaluate the physicochemical stability of concentrated solutions of valproate sodium in polypropylene syringes during 30 days at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Five syringes of 40 mL containing 20 mg/mL of sodium valproate in 0.9% sodium chloride were prepared and stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ during 30 days. Immediately after preparation and periodically during the storage, valproate concentrations were measured by high-performance liquid chromatography. Spectrophotometric absorbance at different wavelengths, pH measurement, and microscopic observations were also performed. All solutions were physically stable during the study period storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. No color change, turbidity, precipitation, or opacity at visual observation was noticed. No significant pH variations or optic densities were observed. No crystals were seen by microscopic analysis. Concentrations of valproate remained stable during the period of storage. Solutions of sodium valproate 20 mg/mL in syringes of 0.9% sodium chloride were physically and chemically stable for at least 30 days when stored in syringes at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. These solutions may be prepared in advance by a centralized intravenous additive service.

Mots-clefs

Diagnosing enterovirus meningitis via blood transcriptomics: an alternative for lumbar puncture?

Bartholomeus E, De Neuter N, Lemay A, Pattyn L, **Tuerlinckx D, Weynants D**, Van Lede K, van Berlaer G, Bulckaert D, Boiy T, Vander Auwera A, Raes M, Van der Linden D, Verhelst H, Van Steijn S, Jonckheer T, Dehoorne J, Joos R, Jansens H, Suls A, Van Damme P, Laukens K, Mortier G, Meysman P, Ogunjimi B

Références	Doi	IF
<i>J Transl Med.</i> 2019 Aug 23;17(1):282	10.1186/s12967-019-2037-6	4,197

Abstract

BACKGROUND: Meningitis can be caused by several viruses and bacteria. Identifying the causative pathogen as quickly as possible is crucial to initiate the most optimal therapy, as acute bacterial meningitis is associated with a significant morbidity and mortality. Bacterial meningitis requires antibiotics, as opposed to enteroviral meningitis, which only requires supportive therapy. Clinical presentation is usually not sufficient to differentiate between viral and bacterial meningitis, thereby necessitating cerebrospinal fluid (CSF) analysis by PCR and/or time-consuming bacterial cultures. However, collecting CSF in children is not always feasible and a rather invasive procedure.

METHODS: In 12 Belgian hospitals, we obtained acute blood samples from children with signs of meningitis (49 viral and 7 bacterial cases) (aged between 3 months and 16 years). After pathogen confirmation on CSF, the patient was asked to give a convalescent sample after recovery. 3' mRNA sequencing was performed to determine differentially expressed genes (DEGs) to create a host transcriptomic profile.

RESULTS: Enteroviral meningitis cases displayed the largest upregulated fold change enrichment in type I interferon production, response and signaling pathways. Patients with bacterial meningitis showed a significant upregulation of genes related to macrophage and neutrophil activation. We found several significantly DEGs between enteroviral and bacterial meningitis. Random forest classification showed that we were able to differentiate enteroviral from bacterial meningitis with an AUC of 0.982 on held-out samples.

CONCLUSIONS: Enteroviral meningitis has an innate immunity signature with type 1 interferons as key players. Our classifier, based on blood host transcriptomic profiles of different meningitis cases, is a possible strong alternative for diagnosing enteroviral meningitis.

Mots-clefs

Beers criteria; Inappropriate prescribing; STOPP/START; nursing homes

Successful laparoscopic management of a hepatic abscess caused by a fish bone.

Beckers G, Magera JP, Poncelet V, Nita T.

Références	Doi	IF
Acta Chir Belg. 2019 Aug 30:1-4 [Epub ahead of print]	10.1080/00015458.2019.1658353	0,521

Abstract

BACKGROUND: Hepatic abscess is a rare condition but comes with heavy consequences if not diagnosed and managed properly. Early detection of this pathology is challenging because of the variety and lack of specificity of symptoms but is necessary for accurate management.

CASE REPORT: We report a case of pyogenic liver abscess secondary to the migration of an ingested fish bone in a 74-year-old female. We used laparoscopic surgery to drain the abscess, remove the foreign body responsible and look for the perforation site. Parenteral antibiotherapy was added to the surgical treatment.

CONCLUSION: Early diagnosis of hepatic abscess caused by the migration of a foreign body remains a challenge. In our opinion, laparoscopic surgery associated with antibiotics is the safest and most effective therapeutic option.

Mots-clefs

Hepatic abscess; fish bone; foreign body; laparoscopic drainage

Respiratory Mandibular Movement Signals Reliably Identify Obstructive Hypopnea Events During Sleep.

Martinot JB, Le-Dong NN, Cuthbert V, Denison S, Borel JC, Gozal D, Pépin JL.

Références

Doi

IF

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3,508

Abstract

CONTEXT: Accurate discrimination between obstructive and central hypopneas requires quantitative assessments of respiratory effort by esophageal pressure (OeP) measurements, which preclude widespread implementation in sleep medicine practice. Mandibular Movement (MM) signals are closely associated with diaphragmatic effort during sleep.

OBJECTIVE: We aimed at reliably detecting obstructive off central hypopneas events using MM statistical characteristics.

METHODS: A bio-signal learning approach was implemented whereby raw MM fragments corresponding to normal breathing (NPB; $n = 501$), central ($n = 263$), and obstructive hypopneas ($n = 1861$) were collected from 28 consecutive patients (mean age = 54 years, mean AHI = 34.7 n/h) undergoing in-lab polysomnography (PSG) coupled with a MM magnetometer, and OeP recordings. Twenty three input features were extracted from raw data fragments to explore distinctive changes in MM signals. A Random Forest model was built upon those input features to classify the central and obstructive hypopnea events. External validation and interpretive analysis were performed to evaluate the model's performance and the contribution of each feature to the model's output.

RESULTS: Obstructive hypopneas were characterized by a longer duration (21.9 vs. 17.8 s, $p < 10^{-6}$), more extreme low values ($p < 10^{-6}$), a more negative trend reflecting mouth opening amplitude, wider variation, and the asymmetrical distribution of MM amplitude. External validation showed a reliable performance of the MM features-based classification rule (Kappa coefficient = 0.879 and a balanced accuracy of 0.872). The interpretive analysis revealed that event duration, lower percentiles, central tendency, and the trend of MM amplitude were the most important determinants of events.

CONCLUSIONS: MM signals can be used as surrogate markers of OeP to differentiate obstructive from central hypopneas during sleep.

Mots-clefs

central hypopnea; hypopnea; mandibular movements; obstructive hypopnea; respiratory effort; sleep apnea syndrome

Effect of lipegfilgrastim administration as prophylaxis of chemotherapy-induced neutropenia on dose modification and incidence of neutropenic events: real-world evidence from a non-interventional study in Belgium and Luxembourg.

Fontaine C, Claes N, Graas MP, Samani KK, Vuylsteke P, Vulsteke C.

Références

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Abstract

OBJECTIVES: This study evaluated the effect of lipegfilgrastim, a glycopegylated granulocyte-colony stimulating factor, used as primary (PP) or secondary prophylaxis (SP) on chemotherapy (CT) treatment modifications, as well as the incidence of CT-induced neutropenic events in adult patients receiving cytotoxic CT with or without biological therapy (BT) for solid and hematological tumors, in routine clinical practice. Other objectives were to characterize the population of lipegfilgrastim-treated cancer patients and safety assessment.

METHODS: This phase 4, prospective, observational study was conducted at 15 centers from Belgium and Luxembourg, between 2015 and 2017.

RESULTS: Of 139 patients, 82.7% had breast cancer and 54.7% were treated with dose-dense regimens. Most received lipegfilgrastim as PP (82.0%) and were at high-risk of febrile neutropenia (FN) (68.3%). FN and grade III/IV neutropenia were reported for 7.9% and 22.3% patients. Among 123 evaluated patients, CT/BT dose modifications were recorded for 33.3% (PP) and 52.4% (SP) of patients receiving lipegfilgrastim; dose reductions, followed by dose delays, were more frequent than omissions. Among 45 patients with dose modifications, FN was reported for 8.8% and 9.1% patients and grade IV neutropenia for 17.6% and 18.2% of patients when lipegfilgrastim was applied for PP and SP, respectively. Adverse events related to lipegfilgrastim occurred for 55 (39.6%) patients; bone pain and back pain were more frequent. Lipegfilgrastim-related serious adverse events were reported for 9 (6.5%) patients.

CONCLUSION: Use of lipegfilgrastim in real-world settings resulted in limited CT dose modifications and low incidences of neutropenic events, with no new safety concerns arising.

Mots-clefs

Lipegfilgrastim; chemotherapy dose modification; chemotherapy-induced neutropenia; febrile neutropenia; real-world evidence

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