Editor's Choice

Rheumatology Around The World … What is New?

Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the Care RA trial

P Verschueren, D De Cock, L Corluy et al.

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Objectives: To compare the efficacy and safety of intensive combination strategies with glucocorticoids (GCs) in the first 16 weeks (W) of early rheumatoid arthritis (eRA) treatment, focusing on high-risk patients, in the Care in early RA trial. **Methods:** 400 disease-modifying antirheumatic drugs (DMARD)-naive patients with eRA were recruited and stratified into high risk or low risk according to classical prognostic markers. High-risk patients (n=290) were randomized to 1/3 treatment strategies: combination therapy for early rheumatoid arthritis (COBRA) Classic (methotrexate (MTX)+ sulfasalazine+60 mg prednisone tapered to 7.5 mg daily from W7), COBRA Slim (MTX+30 mg prednisone tapered to 5 mg from W6) and COBRA Avant-Garde (MTX+leflunomide+30 mg prednisone tapered to 5 mg from W6). Treatment modifications to target low-disease activity were mandatory from W8, if desirable and feasible according to the rheumatologist. The primary outcome was remission (28 joint disease activity score calculated with C-reactive protein <2.6) at W16 (intention-to-treat analysis). Secondary endpoints were good European League Against Rheumatism response, clinically meaningful health assessment questionnaire (HAQ) response and HAQ equal to zero. Adverse events (AEs) were registered. **Results:** Data from 98 Classic, 98 Slim and 94 Avant-Garde patients were analyzed. At W16, remission was reached in 70.4% Classic, 73.6% Slim and 68.1% Avant-Garde patients (p=0.713). Likewise, no significant differences were shown in other secondary endpoints. However, therapy-related AEs were reported in 61.2% of Classic, in 46.9% of Slim and in 69.1% of Avant-Garde patients (p=0.006). **Conclusions:** For high-risk eRA, MTX associated with a moderate step-down dose of GCs was as effective in inducing remission at W16 as DMARD combination therapies with moderate or high step-down GC doses and it showed a more favorable short-term safety profile.

Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicenter, randomized, double blind, non-inferiority trial versus celecoxib

Hochberg MC, et al.

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Objectives: To compare the efficacy and safety of chondroitin sulfate plus glucosamine hydrochloride (CS+GH) versus celecoxib in patients with knee osteoarthritis and severe pain. **Methods:** Double-blind Multicenter Osteoarthritis interVEntion trial with SYSADOA (MOVES) conducted in France, Germany, Poland and Spain evaluating treatment with CS+GH versus celecoxib in 606 patients with Kellgren and Lawrence grades 2–3 knee osteoarthritis and moderate-to-severe pain (Western Ontario and McMaster osteoarthritis index (WOMAC) score ≥301; 0–500 scale). Patients were randomized to receive 400 mg CS plus 500 mg GH three times a day or 200 mg celecoxib every day for 6 months. The primary outcome was the mean decrease in WOMAC pain from baseline to 6 months. Secondary outcomes included WOMAC function and stiffness, visual analogue scale for pain, presence of joint swelling/effusion, rescue medication consumption, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria and EuroQoL-5D. **Results:** The adjusted mean change (95% CI) in WOMAC pain was −185.7 (−200.3 to −171.1) (50.1% decrease) with CS+GH and −186.8 (−201.7 to −171.9) (50.2% decrease) with celecoxib, meeting the non-inferiority margin of −40: −1.11 (−22.0 to 19.8; p=0.92). All sensitivity analyses were consistent with that result. At 6 months, 79.7% of patients in the combination group and 79.2% in the celecoxib group fulfilled OMERACT-OARSI criteria. Both groups elicited a reduction >50% in the presence of joint swelling; a similar reduction was seen for effusion. No differences were observed for the other secondary outcomes. Adverse events were low and similarly distributed between groups. **Conclusions:** CS+GH has comparable efficacy to celecoxib in reducing pain, stiffness, functional limitation and joint swelling/effusion after 6 months in patients with painful knee osteoarthritis, with a good safety profile.

Incidence and antiviral response of hepatitis C virus reactivation in lupus patients undergoing immunosuppressive therapy.

Chen MH, Chen MH, Tsai CY et al.

Lupus. 2015 Feb 16. Pii: 0961203315571465

Objective: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease and usually requires immunosuppressive therapy, which is a major cause of viral reactivation. The incidence and antiviral response in SLE patients with hepatitis C virus (HCV) reactivation is unclear and needs to be investigated. **Methods:** One hundred and sixty-six SLE patients with antibody to HCV (anti-HCV) status were retrospectively reviewed regarding the events of HCV reactivation. Patients with HCV reactivation were treated with pegylated interferon plus ribavirin treatment. The virological response and relapse rate were evaluated. **Results:** Twenty-six patients were positive for anti-HCV. During a mean 8.4 years of follow-up, 10 (38.5%) cases developed HCV reactivation. No clear relationship was noted between immunosuppressive therapy and the HCV reactivation. Eight patients underwent antiviral therapy and the rapid virological response (RVR), early virological response, and sustained virological response (SVR) rates were 37.5%, 87.5%, and 75.0%, respectively. However, late relapse (reappearance of HCV RNA in serum after archiving SVR) was found in two (33.3%) of six patients achieving SVR. The two cases were HCV genotype 1 b concurrent with corticosteroid treatment. **Conclusions:** HCV reactivation in anti-HCV-positive SLE patients was possibly associated with glucocorticoids. The virological response to interferon plus ribavirin treatment is not inferior to the general population. However, monitoring HCV RNA after SVR is necessary for patients concurrent with corticosteroid treatment due to the risk of late relapse.

Multitarget Therapy for Induction Treatment of Lupus Nephritis: A Randomized, Controlled TrialMultitarget Therapy for Induction Treatment of Lupus Nephritis

Zhihong Liu, Haitao Zhang, Zhangsuo Liu et al.

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Background: Treatment of lupus nephritis (LN) remains challenging. **Objective:** To assess the efficacy and safety of a multitarget therapy consisting of tacrolimus, mycophenolate mofetil, and steroid compared with intravenous cyclophosphamide and steroid as induction therapy for LN. **Design:** 24-week randomized, open-label, multicenter study (ClinicalTrials.gov number: NCT00876616). **Setting:** 26 renal centers in China. **Patients:** Adults (age 18 to 65 years) with biopsy-proven LN. **Intervention:** Tacrolimus, 4 mg/d, and mycophenolate mofetil, 1.0 g/d, versus intravenous cyclophosphamide with a starting dose of 0.75 (adjusted to 0.5 to 1.0) g/m^2 body surface area every 4 weeks for 6 months. Both groups received 3 days of pulse methylprednisolone followed by a tapering course of oral prednisone therapy. **Measurements:** The primary end was complete remission at 24 weeks. Secondary end points included overall response (complete and partial remission), time to overall response, and adverse events. **Results:** After 24 weeks of therapy, more patients in the multitarget group (45.9%) than in the intravenous cyclophosphamide group (25.6%) showed complete remission (difference, 20.3 percentage points [95% CI, 10.0 to 30.6 percentage points]; $P<0.001$). The overall response incidence was higher in the multitarget group than in the intravenous cyclophosphamide group (83.5% vs. 63.0%; difference, 20.4 percentage points [CI, 10.3 to 30.6 percentage points]; $P<0.001$), and the median time to overall response was shorter in the multitarget group (difference, −4.1 weeks [CI, −7.9 to −2.1 weeks]). Incidence of adverse events did not differ between the multitarget and intravenous cyclophosphamide groups (50.3% [91 of 181] vs. 52.5% [95 of 181]). **Limitation:** The study was limited to 24 weeks of follow-up. **Conclusion:** Multitarget therapy provides superior efficacy compared with intravenous cyclophosphamide as induction therapy for LN.

Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis.

Guillevin L, Pagnoux C, Karras A et al.

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Background: The combination of cyclophosphamide and glucocorticoids leads to remission in most patients with antineutrophil cytoplasm antibody (ANCA)-associated vasculitides. However, even when patients receive maintenance treatment with azathioprine or methotrexate, the relapse rate remains high. Rituximab may help to maintain remission. **Methods:** Patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after a cyclophosphamide-glucocorticoid regimen were randomly assigned to receive either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22. The primary end point at month 28 was the rate of major relapse (the reappearance of disease activity or worsening, with a Birmingham Vasculitis Activity Score>0, and involvement of one or more major organs, disease-related life-threatening events, or both). **Results:** The 115 enrolled patients (87 with granulomatosis with polyangiitis, 23 with microscopic polyangiitis, and 5 with renal-limited ANCA-associated vasculitis) received azathioprine (58 patients) or rituximab (57 patients). At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio for relapse, 6.61; 95% confidence interval, 1.56 to 27.96; P=0.002). The frequencies of severe adverse events were similar in the two groups. Twenty-five patients in each group (P=0.92) had severe adverse events; there were 44 events in the azathioprine group and 45 in the rituximab group. Eight patients in the azathioprine group and 11 in the rituximab group had severe infections, and cancer developed in 2 patients in the azathioprine group and 1 in the rituximab group. Two patients in the azathioprine group died (1 from sepsis and 1 from pancreatic cancer). **Conclusions:** More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine.

Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping anti rheumatic therapy: interim results from the prospective randomized controlled RETRO study

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Objective: To prospectively analyse the risk for disease relapses in patients with rheumatoid arthritis (RA) in sustained remission, either continuing, tapering or stopping disease-modifying antirheumatic drugs (DMARDs) in a prospective randomised controlled trial. **Methods:** Reduction of Therapy in patients with Rheumatoid arthritis in On going remission is a multicentre, randomised controlled, parallel-group phase 3 trial evaluating the effects of tapering and stopping all conventional and/or biological DMARDs in patients with RA in stable remission. Patients (disease activity score 28 (DAS28)<2.6 for least 6 months) were randomised into three arms, either continuing DMARDs (arm 1), tapering DMARDs by 50% (arm 2) or stopping DMARDs after 6 months tapering (arm 3). The primary endpoint was sustained remission during 12 months. **Results:** In this interim analysis, the first 101 patients who completed the study were analysed. At baseline, all patients fulfilled DAS28 remission and 70% also American College of Rheumatology- European League Against Rheumatism Boolean remission. 82.2% of the patients received methotrexate, 40.6% biological DMARDs and 9.9% other DMARDs. Overall, 67 patients (66.3%) remained in remission for 12 months, whereas 34 patients (33.7%) relapsed. The incidence of relapses was related to study arms (p=0.007; arm 1: 15.8%; arm 2: 38.9%; arm 3: 51.9%). Multivariate logistic regression identified anticitrullinated protein antibodies (ACPA) positivity (p=0.038) and treatment reduction (in comparison to continuation) as predictors for relapse (arm 2: p=0.012; arm 3: p=0.003). **Conclusions:** This randomised controlled study testing three different treatment strategies in patients with RA in sustained remission demonstrated that more than half of the patients maintain in remission after tapering or stopping conventional and biological DMARD treatment. Relapses occurred particularly in the first 6 months after treatment reduction and were associated with the presence of ACPA.

Evaluating drug-free remission with abatacept in early rheumatoid arthritis: Results from the phase 3b, multicenter, randomized, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period

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Objectives: To evaluate clinical remission with subcutaneous abatacept plus methotrexate (MTX) and abatacept monotherapy at 12 months in patients with early rheumatoid arthritis (RA), and maintenance of remission following the rapid withdrawal of all RA treatment. **Methods:** In the *A*ssessing *V*ery *E*arly *R*heumatoid arthritis *T*reatment phase 3b trial, patients with early active RA were randomised to double-blind, weekly, subcutaneous abatacept 125 mg plus MTX, abatacept 125 mg monotherapy, or MTX for 12 months. Patients with low disease activity (Disease Activity Score (DAS)28 (C reactive protein (CRP)) <3.2) at month 12 entered a 12-month period of withdrawal of all RA therapy. The coprimary endpoints were the proportion of patients with DAS28 (CRP) <2.6 at month 12 and both months 12 and 18, for abatacept plus MTX versus MTX. **Results:** Patients had <2 years of RA symptoms, DAS28 (CRP) ≥ 3.2, anticitrullinated peptide-2 antibody positivity and 95.2% were rheumatoid factor positive. For abatacept plus MTX versus MTX, DAS28 (CRP) <2.6 was achieved in 60.9% versus 45.2% (p=0.010) at 12 months, and following treatment withdrawal, in 14.8% versus 7.8% (p=0.045) at both 12 and 18 months. DAS28 (CRP) <2.6 was achieved for abatacept monotherapy in 42.5% (month 12) and 12.4% (both months 12 and 18). Both abatacept arms had a safety profile comparable with MTX alone. **Conclusions:** Abatacept plus MTX demonstrated robust efficacy compared with MTX alone in early RA, with a good safety profile. The achievement of sustained remission following withdrawal of all RA therapy suggests an effect of abatacept's mechanism on autoimmune processes.

Newly approved Treatments for Hepatitis C

Brand Name	Generic Names	Manufacturer Name	Indication
Sovaldi	sofosbuvir	Gilead Sciences approved Dec 2013	SOVALDI is a hepatitis C virus (HCV) polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. *Sovaldi is approved in HCV genotypes 1 and 4, treatment-naive adults in combination with PEG-IFN and ribavirin*
Harvoni	Ledipasvir Sofosbuvir	Gilead Sciences approved Oct 2014	HARVONI is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) inhibitor, and sofosbuvir, an HCV polymerase inhibitor, and is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults Harvoni is the first combination pill approved to treat chronic HCV genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin
Olysio	simeprevir	Janssen approved Nov 2014	OLYSIO is a hepatitis C virus (HCV) protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection *in combination with peg interferon alpha and ribavirin in adults with compensated liver disease, including cirrhosis.*
VIEKIRA PAK	ombitasvir, paritaprevir, ritonavir, and dasabuvir	AbbVie approved Dec 2014	VIEKIRA PAK includes ombitasvir, a hepatitis C virus inhibitor, paritaprevir, a hepatitis C virus protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus polymerase inhibitor. VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

http://hepatitiscnewdrugresearch.com/2015--advances-in-hepatitis-c-therapies.ht

New therapies for psoriatic arthritis

In September 2013, the FDA approved ustekinumab, an interleukin-12/23 inhibitor, for the treatment of active psoriatic arthritis in adults who have not responded adequately to previous treatment with non-biologic DMARDs.[1] The drug was already approved in Europe and the United States for treatment of moderate to severe psoriatic plaques in adults.

In the same month, the FDA also approved the TNF inhibitor certolizumab pegol (Cimzia) for the treatment of active psoriatic arthritis in adults.[2]

The FDA approved Apremilast (Otezla) for treatment of active psoriatic arthritis (PsA) in March 2014. It is a phosphodiesterase-4 (PDE4) inhibitor that is specific for cAMP, resulting in increased intracellular cAMP levels.

Apremilast was evaluated in nearly 1500 patients with PsA. Patients received apremilast 30 mg PO BID plus concomitant therapy with at least one DMARD, methotrexate, leflunomide, oral corticosteroids, or NSAIDs.[3]

1. Brooks M. Ustekinumab approved for psoriatic arthritis in US, Europe http://www.medscape.com/viewarticle/811496. Accessed October 25, 2013.
2. Brooks M. FDA approves certolizumab for psoriatic arthritis. September 30, 2013; http://www.medscape.com/viewarticle/811865.
3. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. Mar 4 2014

New drugs for idiopathic pulmonary fibrosis (IPF)

- Patients with idiopathic pulmonary fibrosis (IPF) now have two new drugs available for treatment, and novel targeted treatments are on the horizon.
- In October 2014, the Food and Drug Administration approved Esbriet (pirfenidone) and Ofev (nintedanib) based on Phase 3 data showing the safety and efficacy of these drugs for the treatment of IPF.
- Both nintedanib and pirfenidone were approved based on their established safety and effectiveness in clinical trials of over 1,200 patients with IPF.These studies showed a significantly improved forced vital capacity (FVC) in patients treated with nintedanib or pirfenidone compared to placebo.[1,2]
- Pirfenidone, which works on multiple pathways involved in scarring of lung tissue, is not recommended for people with severe liver problems or end-stage kidney disease, or those who require dialysis.[1]
- Nintedanib, a kinase inhibitor that blocks multiple pathways involved in scarring of lung tissue, is not recommended in people with moderate to severe liver problems nor in pregnant women.[2]

1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370:2083.
2. Richard L, de Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idioipathic pulmonary fibrosis. N Engl J Med. 2014; 370:2071.