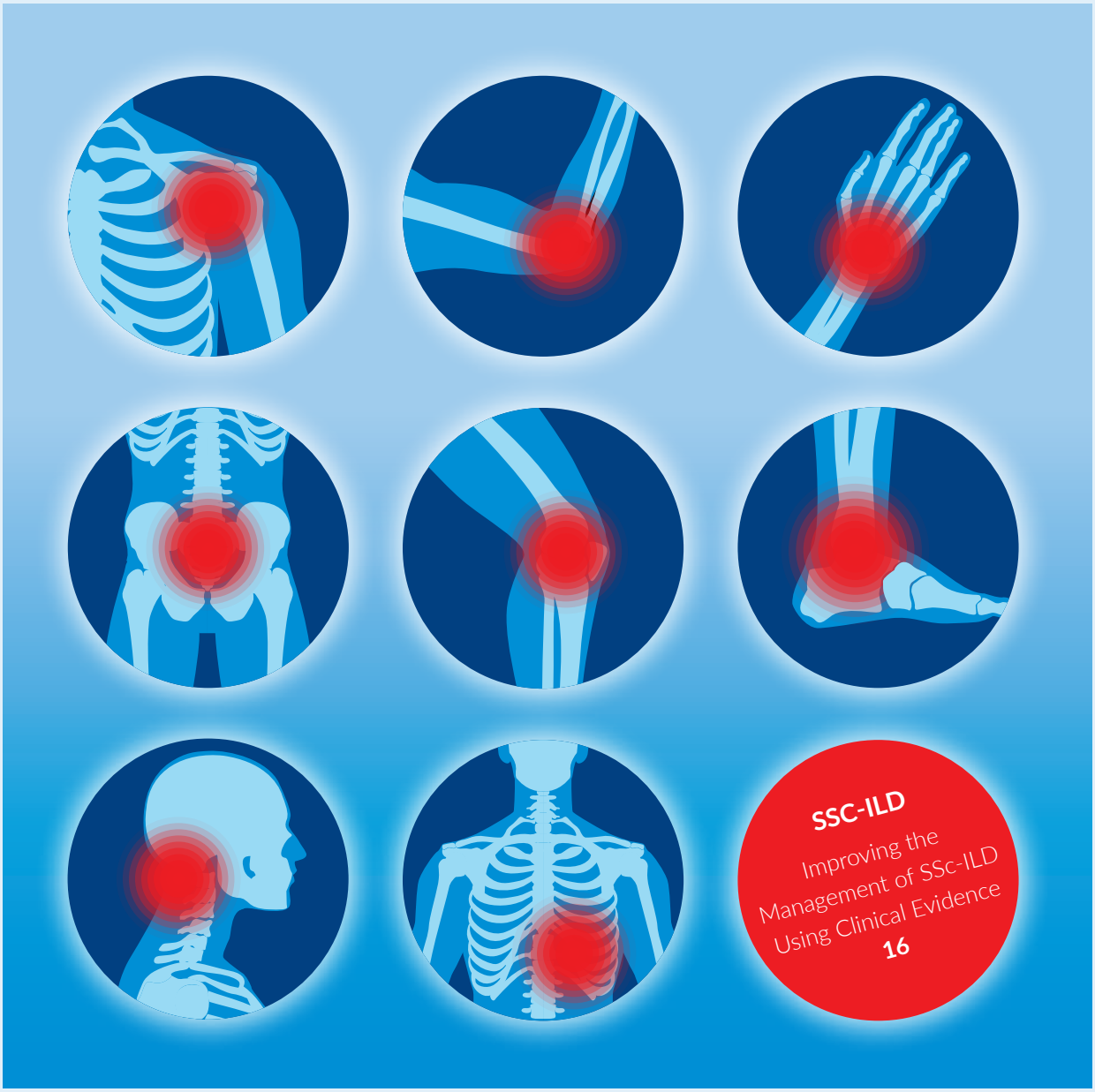
HEALTHBOOK

EULAR HIGHLIGHTS 2021



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6er Packung[2,$]

- 28 Tage Stabilität bei Raumtemperatur [1,2]
- Devices ohne Latex[3]

Benepali™ Etanercept

Imraldi™ Adalimumab

REFERENZEN: 1. BENEPALI™ Fachinformation, Stand: Jan. 2021; abrufbar unter: www.swissmedicinfo.ch. **2.** IMRALDI™ Fachinformation, Stand: Juni 2020; abrufbar unter: www.swissmedicinfo.ch. **3.** Erksine, David et al.: Update on development of biosmilar versions of adalimumab with particular focus on excipients and injection site reactions. Available at: https://www.sps.nhs.uk/wp-content/uploads/2019/01/adalimumab-biosimilar-comparison_updated-Jun-2020.pdf. *BENEPALI™ ist als 2er und 4er Packung erhältlich. $ IMRALDI™ ist als 1er, 2er und 6er Packung erhältlich.

GEKÜRZTE FACHINFORMATION BENEPALI™

Z: Benepali Injektionslösung als Fertigpen/ -spritze zu je 50 mg/1 ml Etanercept oder Fertigspritze zu 25 mg/0.5 ml Etanercept. **I:** Für Erwachsene: aktive rheumatoide Arthritis (RA), wenn Therapie mit DMARDs unzulänglich, Komb. mit Methotrexat (MTX) möglich. Schwere aktive und progressive RA, die zuvor nicht mit Methotrexat behandelt wurde. Aktive, progressive Psoriasis-Arthritis (PA), wenn vorhergehende Therapie mit DMARDs unzulänglich. Schwerer, aktiver Morbus Bechterew (MB), wenn konvent. Therapie unzulänglich. Mittelschwere bis schwere Plaque-Psoriasis (PP). Für Kinder und Jugendliche ≥ 62.5 kg: Juvenile idiopathische Arthritis (JiA): Poly- oder Oligoarthritis oder PA, wenn Therapie mit MTX unzulänglich. Enthesitis-assoziierten Arthritis, wenn konvent. Therapie unzulänglich. Chronische schwere PP, wenn andere systemische Therapie oder Lichttherapie unzulänglich. **D:** Erwachsene: RA: 25 mg zweimal wöchentlich subkutan oder 50 mg einmal wöchentlich. PA und MB: 25 mg zweimal wöchentlich im Abstand von 3 bis 4 Tagen, oder 50 mg einmal wöchentlich. PP: 50 mg pro Woche. Genaueres s. FI. Kinder und Jugendliche ≥ 62.5 kg: JiA: 25 mg zweimal wöchentlich subkutan oder 50 mg einmal wöchentlich. PP bei Kindern und Jugendlichen (ab 6 Jahren): 50 mg einmal wöchentlich für bis zu 24 Wochen. Genaueres s. FI. **KI:** Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile. Sepsis oder Risiko einer Sepsis. Die Behandlung sollte bei Patienten mit aktiven, einschliesslich chronischer oder lokalisierter Infektionen nicht begonnen werden. **VM:** Infektionen (inklusive aktive, als auch inaktive (latente) Tuberkulose und HBV), kongestive Herzinsuffizienz, allergische Reaktionen, hämatologische Reaktionen und ZNS-Störungen sowie höheres Risiko für Lymphome und maligne Erkrankungen sind zu beachten. **IA:** Sulfasalazin, Digoxin, Anakinra. **SS:** Keine Behandl. während S, ausser es ist klar notwendig. Unter Behandl. sollte keine S entstehen. Keine Behandl. während Stillen. **UW:** Sehr häufig: Reakt. an d. Inj.-stelle (inkl. Blutung, Bluterguss, Erythem, Schmerz, Schwellung, Juckreiz), Infekt. (inkl. Infekt. d. oberen Atemwege, Bronchitis, Zystitis, Hautinfekt.). Häufig: Allerg. Reakt., Bildung v. Auto-Ak, Hautausschlag, Pruritus, Pyrexie, Leberenzymerhöhung in Komb. mit MTX. Gelegentliche und (sehr) seltene UW s. FI. **Abgabekategorie B.** Die vollständige FI ist auf www.swissmedicinfo.ch publiziert. Zul-Inh.: Samsung Bioepis CH GmbH, Luzern. Auslieferung: Biogen Switzerland AG, 6340 Baar.

GEKÜRZTE FACHINFORMATION IMRALDI™

Z: IMRALDI™ Injektionslösung als Fertigpen/-spritze zu je 40 mg/0.8 ml Adalimumab. **I:** Für *Erwachsene:* Mässig bis stark ausgeprägte aktive rheumatoide Arthritis (RA) mit unzureichendem Ansprechen auf krankheitsmodifizierende Antirheumatika (DMARDs), in Monotherapie oder in Kombination mit Methotrexat (MTX) bzw. anderen DMARDs; kürzlich diagnostizierte (<3 Jahre) MTX-naive Patienten mit mässig bis stark ausgeprägter RA, in Kombination mit MTX. Psoriasis-Arthritis (PsA) mit ungenügendem Ansprechen auf DMARDs, in Monotherapie oder in Kombination mit DMARDs. Aktive ankylosierende Spondylitis (AS) mit unzureichendem Ansprechen auf herkömmliche Therapien. Morbus Crohn (MC) mit mässiger bis hoher Krankheitsaktivität mit unzureichendem Ansprechen auf herkömmliche Therapien, sowie ungenügendem Infliximab Ansprechen/Unverträglichkeit. Mittelschwere bis schwere aktive Colitis Ulcerosa (UC) mit unzureichendem Ansprechen, Unverträglichkeit oder Kontraindikationen von herkömmlichen Therapien. Mittelschwere bis schwere chronische Plaque Psoriasis (PsO) in Monotherapie, bei denen eine systemische Therapie oder eine PUVA-Therapie angezeigt ist. Aktive mittelschwere bis schwere Hidradenitis suppurativa (HS) mit unzureichendem Ansprechen auf systemische Antibiotikatherapie. Kortikosteroid-abhängige nicht-infektiöse intermediäre oder posteriore Uveitis oder Panuveitis (U) bei unzureichendem Ansprechen auf Kortikosteroide oder Immunmodulatoren; ev. in Kombination mit Kortikosteroiden und/oder Immunmodulatoren. *Jugendliche ab 13 Jahren (mit einer minimalen Körperoberfläche von 1.7* m^2): Polyartikuläre juvenile idiopathische Arthritis (pJIA) mit ungenügendem Ansprechen/Intoleranz auf DMARDs, in Kombination mit MTX oder als Monotherapie (MTX Unverträglichkeit). **D:** Subkutane Injektion. *Erwachsene:* RA, AS, PsA: 40 mg alle zwei Wochen. MC, UC: 160 mg in Woche 0, 80 mg in Woche 2 und danach alle zwei Wochen 40 mg. PsO, U: 80 mg in Woche 0, 40 mg in Woche 1 und danach alle zwei Wochen 40 mg. Bei verminderter Wirkung in UC und RA ist eine Dosisfrequenzerhöhung auf 40 mg wöchentlich möglich. HS: 160 mg in Woche 0, 80 mg in Woche 2 und 40 mg wöchentlich ab Woche 4. *Jugendliche:* pJIA: 40 mg alle zwei Wochen. **KI:** Überempfindlichkeit gegen Inhaltsstoffe, aktive Tuberkulose (TB), schwere Infektionen, mittelschwere bis schwere Herzinsuffizienz (NYHA KI. III-IV). **VM:** Infektionen, einschliesslich opportunistische Infektionen, TB inkl. okulare TB, Hepatitis B Reaktivierung, neurologische Ereignisse einschliesslich demyelinisierende Störungen, allergische Reaktionen einschliesslich anaphylaktische Reaktionen, maligne Tumore inkl. intraokulare Lymphome, Immunsuppression, Impfungen, Lebendimpfungen, Lebendimpfungen bei Neugeborenen nach in utero Exposition, Herzinsuffizienz, gleichzeitige Anwendung von biologischen DMARDs oder anderen TNF-Antagonisten, hämatologische Ereignisse, Auto-Antikörper, Anwendung in der Geriatrie. **IA:** Keine bekannt/nicht untersucht. **SS:** Empfängnisverhütung, Nutzen-Risiko Bewertung. **UW:** Reaktionen an der Injektionsstelle, Infektionen, Leukopenie, Kopfschmerz, Parästhesien, Benommenheit, Husten, Diarrhoe, Motilitätsstörungen, oropharyngeale Schmerzen, Übelkeit, Abdominalschmerzen, Erhöhung der Leberenzyme, Hautausschlag, Dermatitis, Pruritus, Arthritis, muskuloskelettale Schmerzen, Müdigkeit. **Abgabekategorie B.** Die vollständige Fachinformation ist auf www.swissmedicinfo.ch publiziert. Zul-Inh.: Samsung Bioepis CH GmbH, Luzern. Auslieferung: Biogen Switzerland AG, 6340 Baar.

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Für weitere Informationen, siehe Fachinformation von IMRALDI™ auf www.swissmedicinfo.ch.

Scannen Sie den QR-Code für mehr Informationen

Biogen-98310_06.2021

www.biogen.ch

Biogen

EDITORIAL

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Rheumatologisches
Versorgungszentrum Weinfelden
Weinfelden, Switzerland

EULAR 2021: Annual European Congress of Rheumatology

Once again, the 2021 European Alliance of Associations for Rheumatology (EULAR) congress offered a comprehensive overview of the latest groundbreaking research in the field of rheumatology. This edition of *healthbook EULAR Highlights* provides a collection of clinically relevant studies presented at EULAR 2021 held virtually on 2–5 June 2021.

"We seek to deliver world-class education, to provide penetrating and effective advocacy to our political classes, to offer empathetic and comprehensive support to patients and to sustain the research efforts that will ultimately lead to cures for people with rheumatic diseases," underlined the objective of EULAR Prof. Iain McInnes, the EULAR president, in his welcome message.

With COVID-19 vaccines being a recent focus, data from two key studies presented at the congress offered reassurance that adverse reactions to COVID-19 vaccines in patients with rheumatoid diseases were non-serious, with a safety profile similar to that reported for the general population. The vaccines were also fairly effective in most patients with inflammatory rheumatic and musculoskeletal diseases (RMDs), while concomitant rituximab might severely impair the immunogenicity of the vaccines.

There was also a myriad of data in rheumatoid arthritis, psoriatic arthritis and other indications, including the results from the SELECT clinical program and the phase III COMPASS, GO-ALIVE and SENSCIS trials. In addition, the impressive results from the phase III JUNIPERA trial presented during the late-breaking abstract session demonstrated that the benefit of targeting interleukin (IL)-17A might extend to juvenile diseases. Highlights from this year's congress also included long-term follow-up analyses and real-world studies on the effectiveness of biologics.

These and many more highlights are summarized for you in this edition of *healthbook EULAR Highlights*. Join me in celebrating these new insights in rheumatology.

Dr Heino Prillwitz, MD
Rheumatologisches Versorgungszentrum Weinfelden
Weinfelden, Switzerland

ORENCIA® IST ANDERS*

EINZIGARTIGER WIRKMECHANISMUS HEMMT DIE T-ZELL-AKTIVIERUNG[1–4]

- ORENCIA® mit dem Wirksamkeits+ bei ACPA+ RA-Patienten[#,5]
- Schneller Wirkeintritt[°,6]
- Anhaltende Hemmung der radiografischen Progression[6]

* Selektiver Modulator der T-Zell Costimulation. Einzigartiger Wirkmechanismus bei der Behandlung der RA[1–4]
[#] Baseline ACPA-Positivität (vs ACPA-Negativität) war assoziiert mit besserer Response auf Abatacept[5]
[°] Vergleichbar mit Adalimumab

1. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford).2012;51(suppl 5):v3 – v11. doi: 10.1093/rheumatology/kes113. 2. Willemze A. Trouw LA, Toes RE, Huizinga TW. The Influence of ACPA status and characteristics on the cours of RA. Nat Rev Rheumatol. 2012;8(3):144 – 152. 3. Malmström V, Trollmo C, Klareskog L. Modulating co-stimulation: a rational strategy in the treatment of rheumatoid arthritis? Arthritis Res Ther. 2005;7(suppl 2):S15 – S20. 4. ORENCIA® Fachinformation, www.swissmedicinfo.ch 5. Sokolove J et al. Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial. Ann. Rheum. Dis. 2016;75(4):709 – 14. 6. Schiff M, Weinblatt ME et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014; 73: 86 – 94.

Kurzfachinformation ORENCIA® (Abatacept)
I: Rheumatoide Arthritis (RA): Zur Behandlung der vorher mit Methotrexat unbehandelten erosiven rheumatoiden Arthritis bei Erwachsenen in Kombination mit Methotrexat. Zur Reduzierung der Anzeichen und Symptome, zur Besserung der körperlichen Funktionsfähigkeit und zur Reduktion der Progressionsrate struktureller Schäden bei erwachsenen Patienten mit mässiger bis schwerer rheumatoider Arthritis, die auf krankheitsmodifizierende Antirheumatika (DMARDs, disease-modifying anti-rheumatic drugs), wie Methotrexat oder Tumor-Nekrose-Faktor (TNF)-hemmende Substanzen, nicht ausreichend ansprechen. Verwendung in Kombination mit einer DMARD-Therapie, in erster Linie mit Methotrexat. **Polyartikuläre juvenile idiopathische Arthritis (pJIA):** In Kombination mit Methotrexat indiziert zur Behandlung von mässiger bis schwerer aktiver polyartikulärer juveniler idiopathischer Arthritis bei pädiatrischen Patienten ab 6 Jahren, welche auf andere DMARDs (inkl. Methotrexat) nicht ausreichend ansprachen. ORENCIA® wurde bei Kindern unter 6 Jahren nicht untersucht. **D:** ORENCIA® kann als intravenöse (i. v.) Infusion oder als subkutane (s. c.) Injektion verabreicht werden. **Intravenöse Dosierung:** Dosierung bei RA von ~ 10 mg/kg Körpergewicht (KG) i. v., in Woche 0, 2 und 4, danach alle 4 Wochen: < 60 kg KG: 2 Amp. (500 mg); ≥ 60 bis ≤ 100 kg KG: 3 Amp. (750 mg); > 100 kg KG: 4 Amp. (1 g). Dosierung bei Patienten mit pJIA im Alter zwischen 6 und 17 Jahren: < 75 kg KG: 10 mg/kg KG; ≥ 75 kg KG: gemäss Dosierung RA bei Erwachsenen. Maximale Dosis von 1 g. 30-minütige Infusion. **Subkutane Dosierung:** 125 mg wöchentlich unabhängig vom KG. Bei Patienten mit > 100 kg KG: Therapieeinleitung mit einer i. v. Sättigungsdosis gemäss Dosierung RA bei Erwachsenen empfohlen. Anwendung von ORENCIA® s. c. bei Kindern und Jugendlichen nicht geeignet. **KI:** Überempfindlichkeit gegenüber dem Wirkstoff oder einem der Hilfsstoffe gemäss Zusammensetzung. Schwere Infektionen, wie Sepsis und opportunistische Infektionen. **W/VM:** Allergische Reaktionen, Anaphylaxie, anaphylaktoide Reaktionen, Kombination mit biologischen Immunsuppressiva oder Immunmodulatoren, Infektionen, positives Tuberkulosescreening, Virushepatitis, Lebendvakzine, Malignome, Regelmässige Hautuntersuchungen sind für alle Patienten empfohlen, vor allem für diejenigen mit Hautkrebs-Risikofaktoren, chronisch obstruktive Lungenerkrankung (COPD), ältere Patienten, Blutzuckerbestimmung (i. v.), Autoimmunprozesse, Natriumdiät (i. v.). **IA:** Eine gleichzeitige Therapie mit TNF-Blockern ist nicht zu empfehlen. **SS/Stillzeit:** Verwendung bei Schwangeren/stillenden Frauen nicht empfohlen. Bei gebärfähigen Frauen während Behandlung wirksame Empfängnisverhütung erforderlich. **UW** (häufig/sehr häufig): Infektionen des Respirationstrakts; Infektionen des Harntrakts; Herpes Infektionen; Pneumonie; Influenza; Kopfschmerzen; Benommenheit; Hypertonie; erhöhter Blutdruck; Husten; Bauchschmerzen; Diarrhö; Übelkeit; Dyspepsie; Mundulcera; aphtöse Stomatitis; Erbrechen; abnormer Leberfunktionstest; Ausschlag; Ermüdung; Asthenie; lokale Reaktionen an der Injektionsstelle (s. c.); infusionsbedingte Reaktionen: Benommenheit. Pyrexie (bei pädiatrischen Patienten). **P:** Durchstechflasche mit 250 mg Abatacept zur Herstellung einer Infusionslösung. Fertigspritze oder Fertigpen mit 125 mg/ml Abatacept zur subkutanen Anwendung. Abgabekategorie A (Durchstechflasche) oder B (Fertigspritze und Fertigpen). Stand der Information: November 2017. Ausführliche Informationen siehe www.swissmedicinfo.ch. Literatur auf Anfrage. Bristol Myers Squibb SA, Hinterbergstrasse 16, 6312 Steinhausen, www.bms.ch. ORENCIA® ist eine Marke von Bristol Myers Squibb.

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Verpassen Sie nicht die Chance, direkt* mit AMGEVITA® bei RA zu starten!

* Wenn die vorausgegangene antirheumatische Standardtherapie mit krankheitsmodifizierenden Antirheumatika (DMARDs) unzulänglich war.[1]
** AMGEVITA® ist mit Acetat gepuffert.[5]
# Jahrestherapiekosten von Humira® verglichen mit AMGEVITA® (6-Pack; für Humira® ist kein 6-Pack erhältlich).[1,2]

1. AMGEVITA®, www.spezialitätenliste.ch, abgerufen am 25.6.2021. **2.** Humira®, www.spezialitätenliste.ch, abgerufen am 25.6.2021. **3.** Rinvoq®, www.spezialitätenliste.ch, abgerufen am 25.6.2021. **4.** Xeljanz®, www.spezialitätenliste.ch, abgerufen am 25.6.2021. **5.** AMGEVITA® Fachinformation, www.swissmedicinfo.ch.

Kurzfachinformation AMGEVITA® (Adalimumab): Zusammensetzung: Wirkstoff: Adalimumab. **Indikationen:** Erwachsene: Mässig bis stark ausgeprägte aktive rheumatoide Arthritis (RA) mit unzureichendem Ansprechen auf krankheitsmodifizierende Antirheumatika (DMARDs), in Monotherapie oder in Kombination mit Methotrexat (MTX) bzw. anderen DMARDs; kürzlich diagnostizierte (<3 Jahre) MTX-naive Patienten mit mässig bis stark ausgeprägter RA, in Kombination mit MTX. Psoriasis-Arthritis (PsA) mit ungenügendem Ansprechen auf DMARDs, in Monotherapie oder in Kombination mit DMARDs. Aktive ankylosierende Spondylitis (AS) mit unzureichendem Ansprechen auf herkömmliche Therapien. Morbus Crohn (MC) mit mässiger bis hoher Krankheitsaktivität mit unzureichendem Ansprechen auf herkömmliche Therapien, sowie ungenügendem Infliximab Ansprechen/Unverträglichkeit. Mittelschwere bis schwere aktive Colitis Ulcerosa (UC) mit unzureichendem Ansprechen, Unverträglichkeit oder Kontraindikation von herkömmlichen Therapien. Mittelschwere bis schwere chronische Plaque Psoriasis (PsO) in Monotherapie, bei denen eine systemische Therapie oder eine PUVA-Therapie angezeigt ist. Aktive mittelschwere bis schwere Hidradenitis suppurativa (HS) mit unzureichendem Ansprechen auf systemische Antibiotikatherapie. Nicht-infektiöse intermediäre, posteriore oder Panuveitis (U) bei Kortikosteroid-Abhängigkeit oder unzureichendem Ansprechen auf Kortikosteroide oder Immunmodulatoren; nach anatomischem und funktionellem Verlauf in Kombination mit Kortikosteroiden oder Immunmodulatoren. Jugendliche ab 13 Jahren (mit einer minimalen Körperoberfläche von 1.7 m^2): Polyartikuläre juvenile idiopathische Arthritis (pJIA) mit ungenügendem Ansprechen/Intoleranz auf DMARDs, in Kombination mit MTX oder als Monotherapie (MTX Unverträglichkeit). **Dosierung/Anwendung:** Subkutane Injektion. Erwachsene: RA, AS, PsA: 40 mg alle zwei Wochen. MC, UC: 160 mg in Woche 0, 80 mg in Woche 2 und danach alle zwei Wochen 40 mg. PsO, U: 80 mg in Woche 0, 40 mg in Woche 1 und danach alle zwei Wochen 40 mg. Bei verminderter Wirkung in UC, RA und PsO ist eine Dosisfrequenzerhöhung auf 40 mg wöchentlich möglich. HS: 160 mg in Woche 0, 80 mg in Woche 2 und 40 mg wöchentlich ab Woche 4. Jugendliche: pJIA: Bei einer minimalen Körperoberfläche von 1.7 m^2 40 mg alle zwei Wochen. **Kontraindikationen:** Überempfindlichkeit gegen Inhaltsstoffe, aktive Tuberkulose (TB), schwere Infektionen, mittelschwere bis schwere Herzinsuffizienz (NYHA Kl. III-IV). **Warnhinweise und Vorsichtsmassnahmen:** Infektionen, einschliesslich opportunistische Infektionen, TB inkl. okulare TB, Syphilis und Hepatitis B Reaktivierung, neurologische Ereignisse einschliesslich demyelinisierende Störungen, allergische Reaktionen einschliesslich anaphylaktische Reaktionen, maligne Tumore inkl. intraokulare Lymphome, Immunsuppression, Impfungen, Lebendimpfungen, Lebendimpfungen bei Neugeborenen nach in utero Exposition, Herzinsuffizienz, gleichzeitige Anwendung von biologischen DMARDs oder anderen TNF-Antagonisten, hämatologische Ereignisse, Auto-Antikörper, Anwendung in der Geriatrie. Die Nadelkappe des Fertigpens besteht aus trockenem Naturkautschuk (Latex-Derivat), welcher allergische Reaktionen hervorrufen kann. **Interaktionen:** Keine bekannt/nicht untersucht. **Schwangerschaft:** Empfängnisverhütung, Nutzen-Risiko Bewertung. **Unerwünschte Wirkungen:** Reaktionen an der Injektionsstelle, Infektionen, Leukopenie, Kopfschmerz, Parästhesien, Benommenheit, Husten, Diarrhoe, Motilitätsstörungen, Abdominalschmerzen, entzündliche Darmerkrankung, oropharyngeale Schmerzen, Übelkeit, Erhöhung der Leberenzyme, Hautausschlag, Dermatitis, Pruritus, Arthritis, muskuloskelettale Schmerzen, Müdigkeit. **Packungen:** 40 mg/0.8 ml: 1, 2 oder 6 Fertigspritze(n); 1, 2 oder 6 Fertigpen(s) (SureClick). **Abgabekategorie B.** Ausführliche Informationen siehe Arzneimittel-Fachinformation: www.swissmedicinfo.ch.
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AMGEN®

Targeting GM-CSF in **Severe COVID-19 Pneumonia**

■ Granulocyte/macrophage-colony stimulating factor (GM-CSF) is an important modulator of inflammation and autoimmunity and is implicated in driving excessive immune cell infiltration and activation in the lungs.[1–3] In patients with COVID-19 pneumonia and hyperinflammation, GM-CSF may contribute to respiratory failure and death.[4–6] Mavrilimumab is an anti-GM-CSF receptor-α monoclonal antibody, which downregulates inflammatory processes by inhibiting the GM-CSF signaling axis in granulocytes and myeloid cells[7], and is being investigated as a treatment option for rheumatoid arthritis and giant cell arteritis.[8,9] At EULAR 2021, Dr Lara Pupim presented results from Cohort 1 of a phase II/III trial, which evaluated the efficacy and safety of mavrilimumab in patients with severe COVID-19 pneumonia and hyperinflammation and not requiring mechanical ventilation.[10]

Lara Pupim, MD
Kiniksa Pharmaceuticals Corp.
Lexington, MA, USA

Mavrilimumab versus placebo reduced mechanical ventilation and mortality in patients with severe COVID-19

This ongoing global, double-blind study included patients who had confirmed COVID-19 and bilateral pneumonia, with laboratory findings indicative of hyperinflammation.[10] In the phase II portion of the trial, patients were enrolled into 2 cohorts: non-mechanically ventilated patients (Cohort 1; n=116) requiring supplemental oxygen to maintain SpO2 ≥92%; and mechanically ventilated patients (Cohort 2) for whom mechanical ventilation was initiated within 48 hours prior to randomization. Patients were randomized 1:1:1 to receive a single intravenous infusion of either 10 mg/kg mavrilimumab, 6 mg/kg mavrilimumab or placebo. The primary efficacy endpoint was the proportion of patients alive and free of mechanical ventilation at day 29. The key secondary endpoints included time to 2-point clinical improvement on the National Institute of Allergy and Infectious Diseases (NIAID) scale, time to return to room air and mortality at day 29. The prespecified evidentiary standard for phase II endpoints was a 2-sided alpha value of 0.2, without adjustment for multiplicity. In the efficacy analysis, patients were pooled across two dose levels, as there were no apparent differences in outcomes between the two groups.

Mavrilimumab versus placebo reduced mechanical ventilation and death at day 29

Baseline characteristics were balanced across treatment arms.[10] The population was ethnically/racially diverse (43% non-white), 49% were obese (body mass index ≥30) and

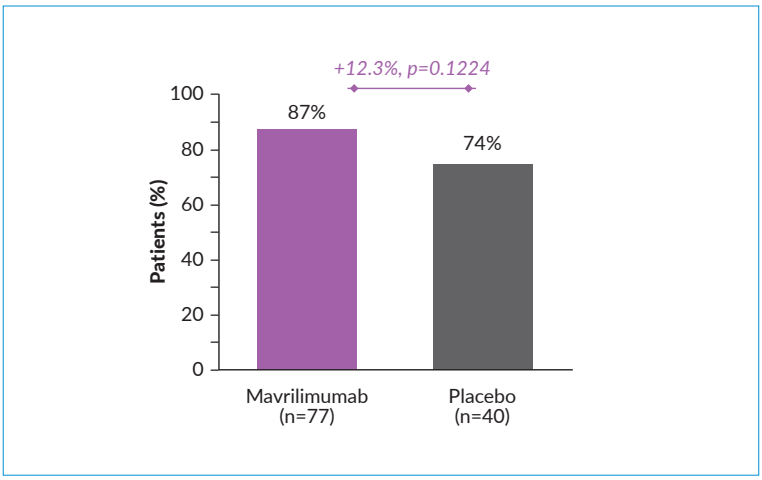
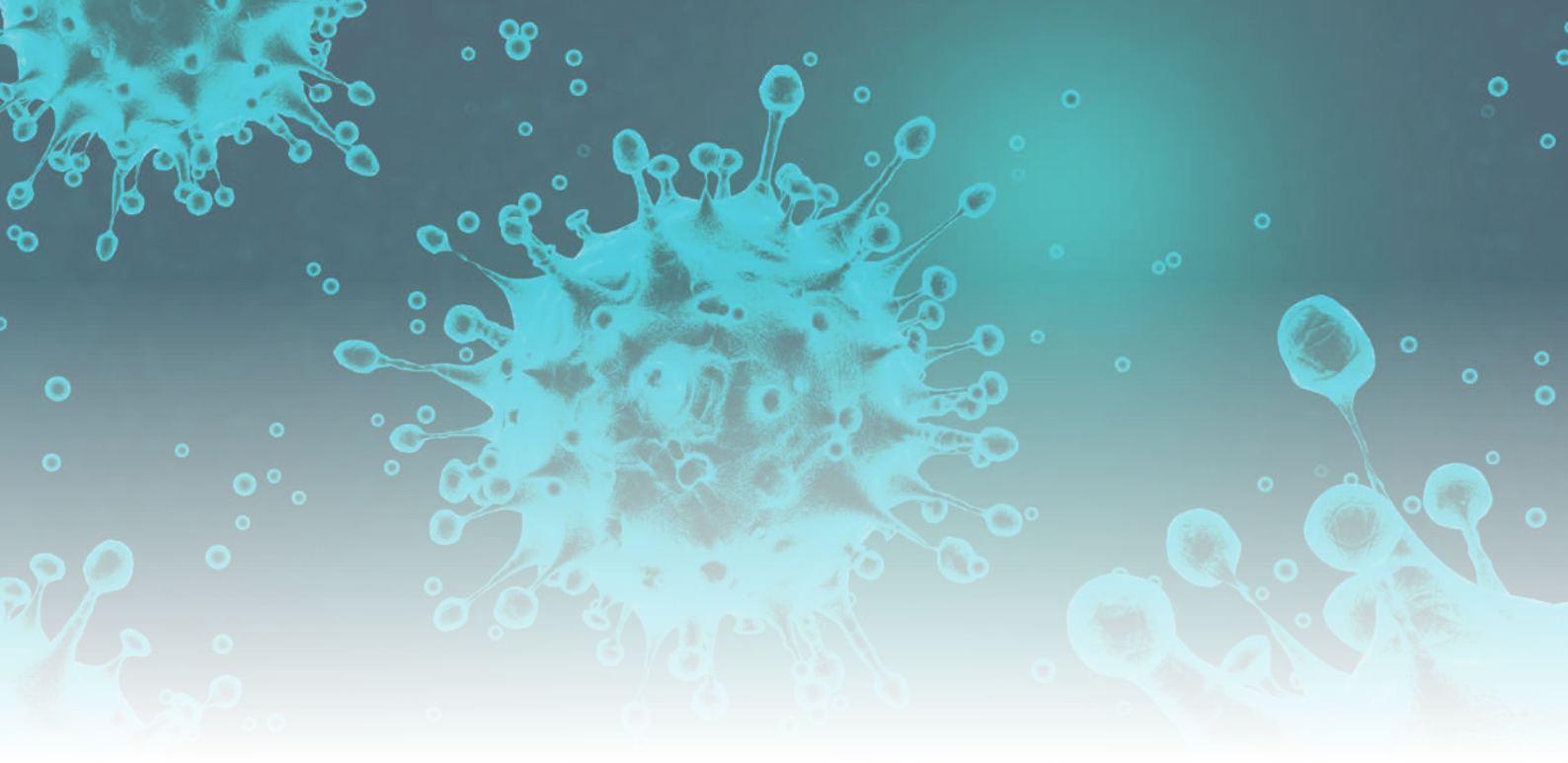


Figure 1. Mavrilimumab improved the proportion of patients alive and free of mechanical ventilation versus placebo. Adapted from Pupim et al. 2021.[10]



29% were >65 years. All patients received local standard of care (SOC) therapy: 96% received corticosteroids or dexamethasone and 29% antivirals/remdesivir.

The trial met its primary endpoint as the proportion of patients alive and free from mechanical ventilation at day 29 was 12.3% higher with mavrilimumab plus SOC compared with placebo plus SOC (84% vs 74%; p=0.1224) (**Figure 1**).[10] There was a lower mortality rate at day 29 among patients who received mavrilimumab compared with placebo (8% vs 21%), corresponding to a 61% reduction in the risk of death (HR: 0.39; p=0.0726). Furthermore, patients receiving mavrilimumab experienced a 65% reduction in the risk of mechanical ventilation or death through day 29 versus placebo (HR: 0.35; p=0.0175).

Patients receiving mavrilimumab also showed a trend towards a faster time to 2-point clinical improvement compared with placebo (median time: 7 days vs 11 days) and faster median time to room air (7 days vs 9 days), but this trend did not reach statistical significance.

Mavrilimumab was well tolerated

Mavrilimumab was generally well tolerated at both dose levels, with no drug-related serious adverse events (AEs) reported.[10] Overall, fewer AEs occurred among mavrilimumab-treated patients compared with those treated with placebo. There were also fewer deaths among patients receiving mavrilimumab versus placebo (9% vs 22.5%). Secondary infections occurred less frequently in the mavrilimumab 10 mg/kg and 6 mg/kg treatment arms (11.4% and 9.8%) versus the placebo arm (22.5%). Thrombotic events, a known complication of COVID-19, occurred only in the placebo arm (12.5%).

CONCLUSIONS

- In non-mechanically ventilated patients with COVID-19 pneumonia and hyperinflammation, mavrilimumab reduced the risk of mechanical ventilation and death at day 29 compared with placebo.[10]
- Mavrilimumab was well tolerated with a favorable safety profile.

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COVID-19 Vaccine in Patients with **Rheumatic and Musculoskeletal Disease**

■ Vaccines are a pillar of good public health, as they can prevent various serious diseases and thus save millions of lives every year. However, the safety of vaccines is questioned in patients with inflammatory rheumatic and musculoskeletal diseases (RMDs) and/or patients treated with immunomodulatory drugs.[1] At EULAR 2021, Dr Pedro M. Machado presented safety data from the EULAR COVID-19 Vaccination (COVAX) Registry, which included RMD patients receiving COVID-19 vaccines.[1,2]

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University College London
Northwick Park Hospital
London, UK

The favorable safety profile of COVID-19 vaccines in patients with inflammatory RMDs versus the general population

COVAX is an observational registry which launched in February 2021.[1,2] Patients were eligible for inclusion if they had RMDs and were vaccinated for COVID-19.

COVID-19 vaccines were tolerated by the majority of RMD patients, with rare reports of disease flares

At data cutoff, 1,519 patients have been reported in the registry.[1] About 2/3 of patients were female and the mean age was 63 years, ranging from 15 to 97 years. A total of 28 countries have contributed to the registry, with France and Italy being the largest contributors. Half of the patients (51%) had inflammatory joint diseases, 19% had connective tissue diseases, 16% had vasculitis and 4% had other immune-mediated inflammatory diseases, while 9% of patients had non-inflammatory RMDs.[1] Regarding individual diagnoses, the most frequent was rheumatoid arthritis (30%), followed by axial spondylarthritis (8%), psoriatic arthritis (8%), systemic lupus erythematosus (SLE) (7%) and polymyalgia rheumatica (6%).

At the time of vaccination, 45% of patients were treated with conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs), 36% of patients with biologic DMARDs (bDMARDs) and 31% with systemic glucocorticoids, among other treatments.[1] The most frequent individual DMARDs were methotrexate (29%), tumor necrosis factor (TNF)-inhibitors (18%), antimalarials (10%), rituximab (6%) and mycophenolate (4%). Of note, the most frequently administered COVID-19 vaccine was Pfizer/BioNTech (78%). As of 27 April 2021, 66% of patients had received two doses of the vaccine.

Disease flares following vaccinations occurred in 5% of patients with inflammatory RMDs, with 1.2% of the cases classified as severe flares.[1,2] The most common disease flares were arthritis (2.5%), arthralgia (2.1%), cutaneous flare (0.8%) and increase in fatigue (0.8%) (**Figure 1**). Adverse events (AEs) of any type were reported by 31% of patients and were typically early events, manifested within 7 days after receiving the vaccine. These included pain at the site of infection (19%), fatigue (11%), headache (7%) and generalized muscle pain (6%). Organ or systemic AEs of special interest were reported by 2% of the patients (n=33), with only 2 patients (0.1%) reporting severe AEs. Of these, one patient with systemic sclerosis/SLE overlap syndrome experienced a transient hemiparesis, while in the second case, an osteoarthritis patient suffered from vasculitis.

CONCLUSIONS

- The safety profile of COVID-19 vaccines in patients with inflammatory rheumatic and musculoskeletal diseases (RMDs) was reassuring, with most adverse events (AEs) overlapping with those reported in the general population.[1]
- Most patients tolerated the vaccine, with only rare reports of inflammatory flares and very rare events of severe AEs.
- COVID-19 vaccines should be confidently promoted for use in RMD patients, including those with inflammatory RMDs and/or taking immunomodulatory treatments.

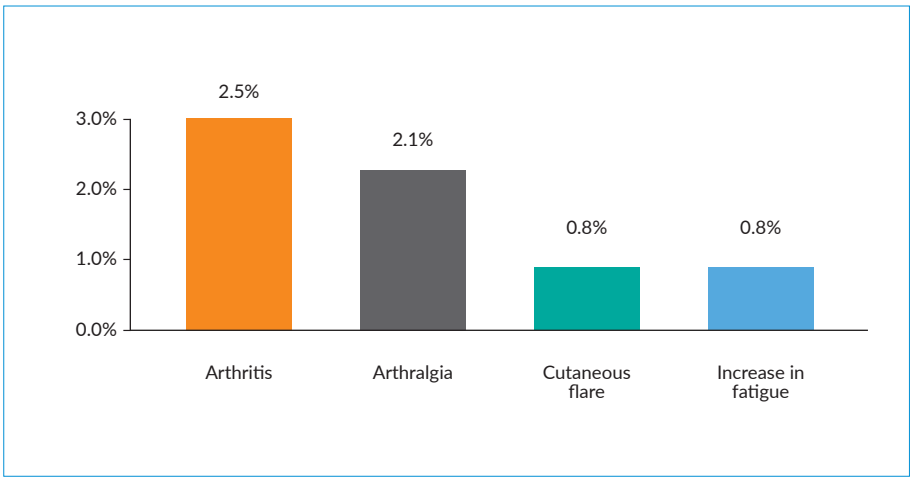

Figure 1. Percentage of disease flares in patients with inflammatory rheumatic diseases (RMDs) after receiving COVID-19 vaccines. Adapted from Machado et al. 2021.[1]

[1] Machado PM et al. COVID-19 vaccine safety in patients with rheumatic and musculoskeletal disease. EULAR 2021 Virtual Congress; 2–5 June 2021. Oral presentation LB0002.
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Referenzen: 1. Fachinformation SIMPONI® (Golimumab), www.swissmedicinfo.ch. **2.** Deodhar A et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. Ann Rheum Dis. 2015;74(4):757–761 and online supplement. **3.** Kavanaugh A et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis. 2014;73(9):1689–1694. **4.** Keystone E.C. et al. Safety and Efficacy of Subcutaneous Golimumab in Patients with Active Rheumatoid Arthritis despite Methotrexate Therapy: Final 5-year Results of the GO-FORWARD Trial. J Rheumatol. 2016;43:298–306. Kopien der Studienpublikationen können bei Bedarf unter der unten angegebenen Adresse angefordert werden.

Kurzfachinformation SIMPONI® (Golimumab). Simponi®: W: Golimumab. **I:** Erw.: mittelschwere bis schwere aktive rheumatoiden Arthritis **(RA)** bei unzureichendem Ansprechen auf krankheitsmodifizierende Antirheumatika (DMARDs, einschliesslich MTX) und bei schwerer, aktiver und progredienter RA ohne MTX-Vorbehandlung; Axiale Spondyloarthritis **(AxSpA):** schwere, aktive ankylosierende Spondylitis **(AS),** die auf eine konventionelle Therapie unzureichend ansprach sowie bei schwerer, aktiver nicht-radiographischer axialer Spondyloarthritis **(nr-axiale SpA)** mit objektiven Anzeichen einer Entzündung mit erhöhtem C-reaktivem Protein und Magnetresonanztomographie-Befund, die auf nichtsteroidale entzündungshemmende Medikamente (NSAR) unzureichend ansprachen; aktive und fortschreitende Psoriasis-Arthritis **(PsA)** nach unzureichendem Ansprechen auf antirheumatische Basistherapie (DMARD-Therapie); mässige bis schwere, aktive Colitis ulcerosa **(CU),** die auf eine konventionelle Therapie (inkl. Kortikosteroiden und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA)) unzureichend ansprach; **D:** s.c. Injektion; RA, AxSpA, PsA: 50 mg einmal im Monat, bei Körpergewicht > 100 kg ist eine Erhöhung der Dosis von Golimumab auf 100 mg einmal monatlich abzuwägen; CU: Körpergewicht ≥ 80 kg: Initial 200 mg gefolgt von 100 mg nach 2 Wochen und danach alle 4 Wochen 100 mg; Körpergewicht < 80 kg: initial 200 mg anschliessend 100 mg nach 2 Wochen, danach 50 mg alle 4 Wochen ab Woche 6 oder bei ungenügendem Ansprechen bis Woche 6 und danach alle 4 Wochen 100 mg; **KI:** SIMPONI® darf nicht angewendet werden bei einer Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile, bei aktiver Tuberkulose (TB) oder anderen schweren Infektionen wie einer Sepsis und opportunistischen Infektionen, bei mittelschwerer oder schwerer Herzinsuffizienz (NYHA-Klasse III/IV); **WH:** Infektionen; latente TB (prophylaktische tuberkulostatische Therapie empfohlen), Hepatitis-B (HBV)-Reaktivierung, Lymphome und Malignome, Leukämie, COPD, Kolondysplasie/-karzinom; Hautkrebs (nicht-melanomatös, Melanom und Merkelzellkarzinom); dekompensierte Herzinsuffizienz, Neurologische Ereignisse, chirurgischer Eingriff, Immunsuppression, Autoimmunprozesse, hämatologische Reaktionen, gleichzeitige Anwendung mit anderen Biologika, Lebendimpfstoffe/infektiöse therapeutische Agenzien, Überempfindlichkeitsreaktionen, Latexempfindlichkeit. Eine Überwachung ist erforderlich bei allen Patienten auf das Auftreten von Infektionen, einschliesslich Sepsis und Tuberkulose, auf das Neuauftreten oder eine Verschlechterung einer Herzinsuffizienz, auf anaphylaktische oder andere schwerwiegende allergische Reaktionen, sowie regelmässige Hauntuntersuchungen, besonders für solche mit Risikofaktoren für Hautkrebs und sowie bei HBV-Trägern auf Hepatitis B. **S/S:** Verabreichung nur, wenn eindeutig medizinisch indiziert, Empfängnisverhütungsmassnahmen über ≥ 6 Monate nach letzter Behandlung, nicht stillen während ≥ 6 Monaten nach letzter Behandlung, Säuglinge: Lebendimpfstoffe erste 6 Monate nach Geburt nicht empfohlen; **UAW:** Sehr häufig: Infektion der oberen Atemwege (Nasopharyngitis, Pharyngitis, Laryngitis und Rhinitis); **P:** Packungen mit 1 Fertigspritze oder 1 Fertigpen à 50 mg oder 100 mg; **AK:** B; **Z:** MSD Merck Sharp & Dohme AG, Werftestrasse 4, CH-6005 Luzern; (V3.0); CH-GOL-00003.

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BNT162b2 Vaccine in **Patients with AIIRDs**

■ Patients with autoimmune inflammatory rheumatic diseases (AIIRDs) are being prioritized for urgent vaccination to mitigate risks of COVID-19.[1] However, patients with a history of autoimmune diseases and those treated with immunosuppressants were excluded from the Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) vaccine trials.[2–4] As such, mRNA vaccine data in patients with AIIRDs are limited. At EULAR 2021, Dr Victoria Furer reported the results of an observational study, which investigated the immunogenicity, efficacy and safety of BNT162b2 vaccine responses in patients with AIIRDs compared with the general population.[5]

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Tel Aviv Medical Center
Tel Aviv, Israel

mRNA COVID-19 vaccine adequately protects patients with AIIRDs

This prospective, multicenter, phase IV study included 686 adult patients with a wide range of AIIRDs such as rheumatoid arthritis (RA) (n=263), psoriatic arthritis (PsA) (n=167), systemic lupus erythematosus (SLE) (n=102), axial spondylarthritis (AxSpA) (n=74), vasculitis (n=73) and idiopathic inflammatory myositis (IIM) (n=19).[5] The control group consisted of a sample of the general population (n=121) without a history of autoimmune disease and immunosuppressive treatment. Pregnant women and people with past vaccination allergies or previous COVID-19 infection were excluded.

All patients received two doses of the BNT162b2 vaccine 3 weeks apart.[5] Immunogenicity was assessed 2–6 weeks after the second dose using a SARS-CoV-2 antitrimeric S1/S2 spike glycoprotein antibody assay (specificity/sensitivity >98%). Seropositivity was defined as >15 binding antibody units (BAU)/mL.

High seropositivity rate with BNT162b2 vaccine

The median age of the patients and the healthy controls was 59 years and 49.5 years, respectively.[5] In both subgroups, about 2/3 of patients were female. The majority (95.2%) of patients with AIIRDs were treated with a wide range of immunosuppressants, including methotrexate (MTX) (25.66%), antitumor necrosis factors (TNFs) (25.07%) and glucocorticoids (18.95%).

The overall seropositivity rate was 86% (n=590) among AIIRDs patients versus 100% among controls (p<0.0001).[5] Patients with AIIRDs had lower titers of S1/S2 antibody compared with controls (mean, 218.6 BAU/mL vs 132.9 BAU/mL). Results further showed that patients receiving rituximab

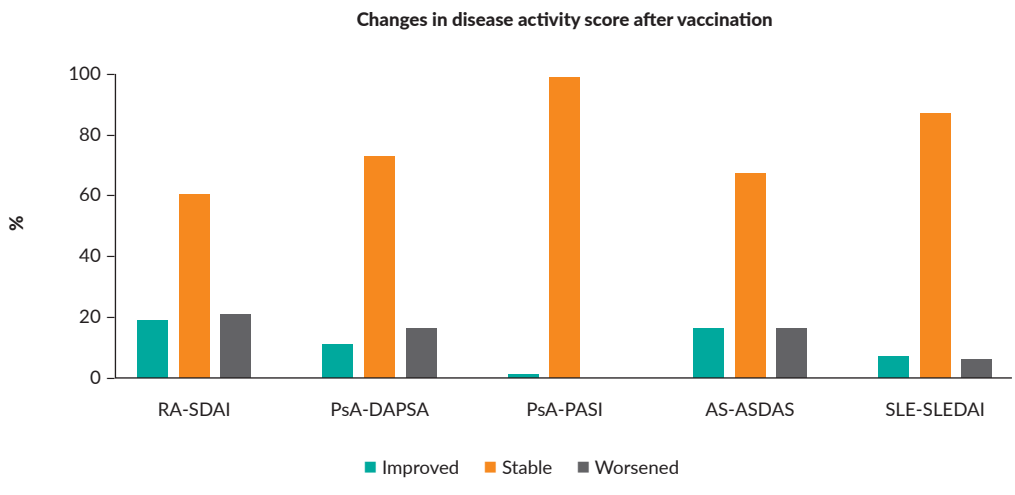

Figure 1. Vaccination effect on disease activity in patients with autoimmune inflammatory rheumatic diseases (AIIRDs). AS, axial spondyloarthritis; ASDAS, Ankylosing Spondylitis Disease Activity Score; DAPSA, Disease Activity in Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Adapted from Furer et al. 2021.[5]

(n=87) versus other treatments had the lowest seropositivity rate (39%), suggesting that anti-CD20 therapy significantly impaired immunogenicity. The time interval between pre-vaccination administration of rituximab and vaccination had a significant impact on the vaccine's immunogenicity (after 6 months: 18.39% seropositive; after 1 year: 52.18% seropositive).

Patients treated with IL-6, IL-17 and TNF inhibitors as monotherapy had an immunogenicity response comparable with controls.[5] However, treatment with rituximab (p<0.0001), glucocorticoids (p=0.0151), mycophenolate mofetil (MMF) (p=0.0013) and abatacept (p=0.0007), particularly when used in combination with MTX, considerably reduced immunogenicity.

Multivariate regression analysis showed that age >65 years, the presence of rheumatoid arthritis, IIM, anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitis and other vasculitides, as well as treatment with rituximab, glucocorticoids, MMF, anti-CD20 antibodies and abatacept, were associated with a lower rate of seropositivity.[5] In terms of efficacy of vaccination, 1 patient in the AIIRD cohort died as a result of symptomatic COVID-19 disease, while 1 control subject was diagnosed with mild COVD-19 and fully recovered.

Vaccination with BNT162b2 was safe

Mild adverse events (AEs) occurred at a similar rate among patients with AIIRDs and control subjects.[5] In the AIIRD group, there were AEs of special interest: herpes zoster (n=6), uveitis (n=2), herpes labialis and pericarditis (each n=1). Overall, 3 patients died after the second vaccine dose: 1 with psoriatic arthritis and comorbid cardiovascular disease had a fatal myocardial infarction; 1 with a history of systemic vasculitis who developed severe vasculitis and died after developing sepsis; 1 after contracting COVID-19. In patients with RA, PsA, AxSpA and SLE, post-vaccination indices of disease activity remained stable (**Figure 1**).

CONCLUSIONS

- This multicenter, real-life study demonstrated a high seropositivity rate to the Pfizer/BioNTech mRNA vaccine among patients with autoimmune inflammatory rheumatic diseases (AIIRDs) versus controls.[5]
- Immunogenicity was severely impaired by rituximab, moderately impaired by glucocorticoids, abatacept and mycophenolate mofetil (MMF), particularly when used in combination with methotrexate (MTX).
- The vaccine was well tolerated and post-vaccination disease activity was stable in most AIIRD patients.

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Targeting IL-17A in **Juvenile Idiopathic Arthritis**

■ Secukinumab is a fully human anti-interleukin (IL)-17A antibody, which demonstrated efficacy and safety in adult patients with psoriatic arthritis (PsA), ankylosing spondylitis and non-radiographic axial spondyloarthritis (axSpA).[1–3] At EULAR 2021, Dr Ruperto presented primary results from the phase III JUNIPERA study that assessed secukinumab in enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA), the pediatric correlates of axSpA and PsA, respectively.[4]

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Gaslini Children's Hospital
Genova, Italy

JUNIPERA: Secukinumab delays time to flare in children with enthesitis-related arthritis and juvenile psoriatic arthritis

In this study, open-label secukinumab was subcutaneously administered (75 mg in patients <50 kg and 150 mg in patients ≥50 kg) at baseline and weeks 1, 2, 3, 4, 8 and 12 in treatment period 1.[4] Those who achieved at least juvenile idiopathic arthritis (JIA) American College of Rheumatology (ACR) 30 response by week 12 were included in double-blinded treatment period 2. In this period, patients were randomized 1:1 to receive either secukinumab or placebo every 4 weeks until a disease flare or up to week 104. The trial included patients aged 2 to <18 years with ERA or JPsA and ≥6 months active disease duration. The primary endpoint was time to flare in treatment period 2, while key secondary endpoints included JIA ACR 30/50/70/90/100, inactive disease, Juvenile Arthritis Disease Activity Score (JADAS), enthesitis count and safety.

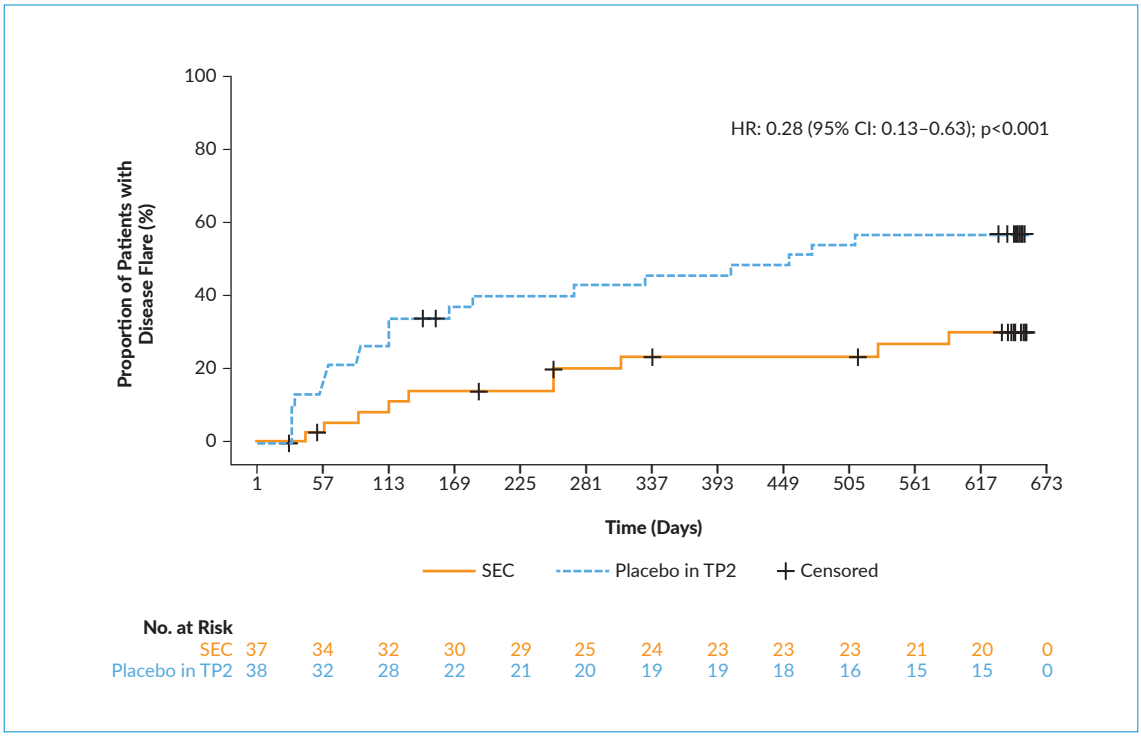

Figure 1. Time to disease flare with secukinumab versus placebo in treatment period 2. SEC, secukinumab; TP, treatment-period. Adapted from Ruperto et al. 2021.[4]

Significantly longer time to flare

In the open-label portion of the study, a total of 86 patients were enrolled, 52 patients with ERA and 34 patients with JPsA.[4] The mean age was 13.1 years and 1/3 of the patients were female. Patients had high disease activity at baseline with a mean JADAS-27 of 15.1 and mean enthesitis count of 2.6.

At the end of 12 weeks of study period 1, 75 patients (90.4%) achieved JIA ACR30 and 58 patients (69.9%) achieved JIA ACR70.[4] After randomization to study period 2 corresponding to withdrawal study design, 37 patients received secukinumab and 38 received placebo in the double-blinded period. Results of treatment period 2 showed 10 flares among the secukinumab-treated patients, as compared with 21 flares among placebo-treated patients. Importantly, patients in the secukinumab arm had a significantly longer time to flare, with a 72% reduction in the risk of flare (HR: 0.28 [95% CI: 0.13–0.63]; p<0.001) (**Figure 1**).

Non-responder imputation (NRI) analyses further showed that 87.2%, 83.7%, 67.4%, 38.4%, and 24.4% of patients achieved JIA ACR 30/50/70/90/100, respectively, while 34.9% achieved inactive disease.[4] The greatest JADAS-27 improvement was observed in treatment period 1, suggesting that most of the reduction in disease activity occurred during the initial 12 weeks of secukinumab treatment with sustained reduction during treatment period 2 up to week 104. Among patients with ERA, 73.9% experienced complete resolution of the enthesis, while 3/5 patients with dactylitis experienced complete resolution of this condition.

The favorable safety profile

No new safety signals with secukinumab were observed.[4] Rates of any adverse events (AEs) (91.7% vs 92.1%) and serious AEs (14.6% vs 10.5%) between the secukinumab and the placebo groups were comparable for the entire treatment, with nasopharyngitis being the most common treatment-emergent AE (33.3% vs 28.9%). Treatment discontinuation due to AEs was reported in 3 patients (6.3%) treated with secukinumab and 5 patients (13.2%) treated with placebo.

CONCLUSIONS

- In pediatric patients with enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA), secukinumab demonstrated a significantly longer time to flare versus placebo.[4]
- Sustained improvements in signs and symptoms on joints, enthesitis and dactylitis were observed through week 104.

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Improving the Management of SSc-ILD Using Clinical Evidence

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a common manifestation and a leading cause of morbidity and mortality in patients with SSc.[1-4] Early diagnosis, severity assessment, progression monitoring and appropriate treatment of SSc-ILD are key to achieving an efficacious and optimal outcome.[5] At EULAR 2021, during the symposium organized by Boehringer Ingelheim, Prof. Anna-Maria Hoffmann-Vold discussed how to improve the journey for patients with SSc.[6] In another presentation, Prof. Toby M. Maher presented the diagnostic work-up and new treatment modalities for SSc and lung involvement.[7] Finally, Dr Elizabeth R. Volkmann presented the recent analysis of the SENSCIS trial assessing nintedanib (Ofev®)[8] in SSc-ILD patients with and without dyspnea at baseline.[9]

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Diagnostic work-up in SSc-ILD

At the time of SSc diagnosis, all patients should be examined for disease-specific organ manifestations including ILD, which is a frequent complication of SSc.[2,10,11] Data of the EUSTAR cohort showed that about 35% of patients with limited cutaneous (lc) SSc and 53% of patients with diffuse cutaneous (dc) SSc had ILD, while in the Norwegian cohort, the incidence of ILD was 75% in patients with dcSSc and 45% in patients with lcSSc.[2,10] The longitudinal EUSTAR study further demonstrated that ILD appears early in the course of SSc. Among patients who developed SSc 1 year after the onset of Raynaud's phenomenon, more than 90% of patients had impaired diffusing capacity of the lungs for carbon monoxide (DLCO) <80% of predicted, with 65% of patients within the first year (**Figure 1**).[11] The incidence rate of forced vital capacity (FVC) <80% of predicted was 31% during the first year.

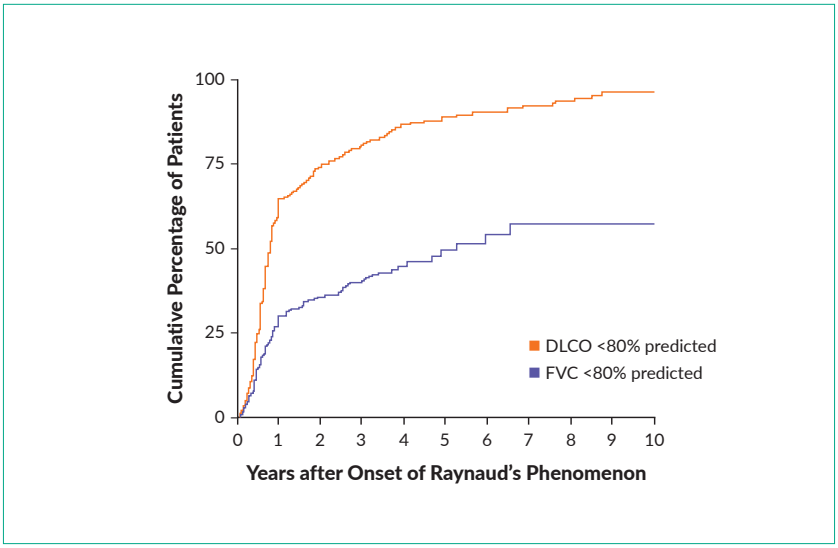

Figure 1. Kaplan-Meier curves of incident pulmonary involvement in patients with systemic sclerosis from EUSTAR after the onset of Raynaud's phenomenon. DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity. Adapted from Jaeger et al. 2016.[11]

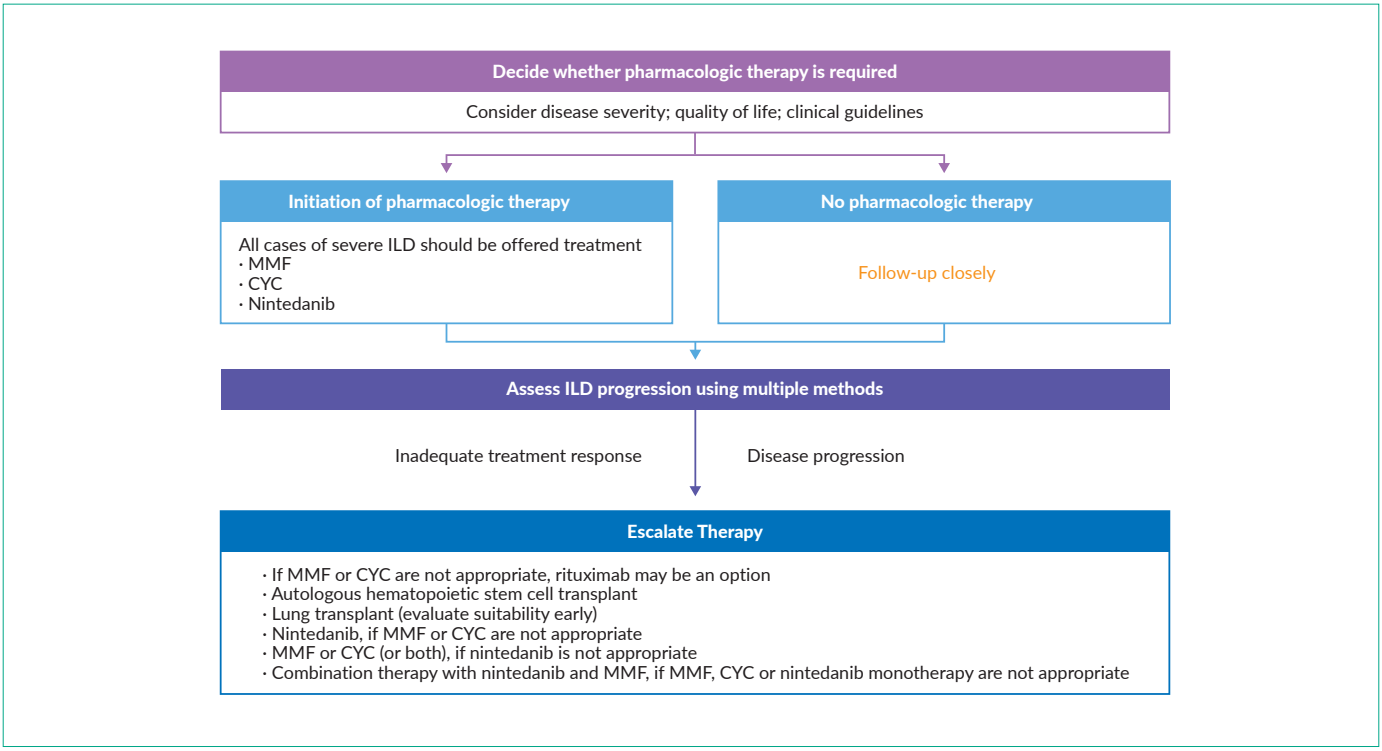

Figure 2. Evidence-based consensus recommendation for the treatment of SSc-ILD. CYC, cyclophosphamide; MMF, mycophenolate mofetil; SSc-ILD, systemic sclerosis-associated interstitial lung disease. Adapted from Hoffmann-Vold et al. 2020.[5]

By using a modified Delphi process, a large study established the first evidence-based European consensus for SSc-ILD management in six key domains, including risk factors, screening, diagnosis and severity assessment, treatment initiation and options, disease progression assessment and treatment escalation, as well as developed an SSc-ILD management algorithm for use in clinical practice.[5] Many factors associated with an increased risk of developing ILD in patients with SSc were identified, such as preexisting respiratory symptoms, smoking history and certain ethnicities, along with male gender, the presence of dcSSc and anti-topoisomerase I antibodies.[12–16] Of those who might be at risk of developing ILD, the guidelines suggest that patients should be screened at baseline using high-resolution computed tomography (HRCT)[16–18], with pulmonary function tests including FVC and DLCO and auscultation as supporting diagnostic tools.[19,20] After obtaining baseline parameters for diagnosis, screening with pulmonary function tests should be repeated regularly[19,20], while the frequency of screening and use of HRCT should be determined by a clinician.[21–23]

The importance of HRCT as the primary tool for diagnosis of SSc-ILD was demonstrated in a study that assessed the performance of pulmonary function tests versus HRCT of the chest for the detection of SSc-ILD in clinical practice.[24] Among 102 patients included in this study, 64 (63%) showed significant ILD on HRCT, while only 27 (26%) had an FVC <80% of predicted. Of the 64 patients with significant ILD on HRCT, 40 (63%) had a normal FVC value; of these, 5 patients had severe, functionally occult lung fibrosis, with 2 patients having the results of all pulmonary function tests within normal limits. These results indicate a high risk of missing significant SSc-ILD when using pulmonary function tests alone in the early detection and screening of SSc-ILD in clinical practice.

At the time of ILD diagnosis, the severity of the disease should be assessed using more than one measure.[5] These include changes in the extent or pattern of fibrosis on HRCT, FVC and DLCO values, as well as clinical symptoms, exercise-induced oxygen desaturation on the 6-minute walk test and quality of life.[23,25,26] In addition, it is important to estimate the risk of ILD progression, measured as an FVC decline over time, at diagnosis.[25]

Evidence-based consensus for the treatment of SSc-ILD

Various factors drive treatment initiation: patients' symptoms, quality of life and clinical guidelines (**Figure 2**).[5] Based on European recommendations, all patients with SSc and severe or progressive ILD should be offered pharmacological treatment with mycophenolate mofetil (MMF), cyclophosphamide or nintedanib. When assessing the appropriate treatment options, several parameters should be considered, including scientific evidence of efficacy and safety, prolonged time to progression, rate of improvement of patient's symptoms and previous clinical experience. In this regard, cyclophosphamide and MMF have been the mainstay of SSc-ILD treatment, based on data from the Scleroderma Lung Study (SLS) I[27] and SLS II[28], which demonstrated that both drugs are associated with improved lung function as measured by FVC, although MMF was better tolerated. Recently, interest has focused on biological therapeutics, including rituximab[29–31] and tocilizumab[32,33], which showed promising results in lowering the rate of declining pulmonary function in patients with SSc-ILD. The antifibrotic therapy with nintedanib was investigated in the phase III SENSCIS[34] and INBUILD[35] trials, which both demonstrated that nintedanib significantly reduced the annual rate of FVC decline of patients with SSc-ILD, as compared with placebo.

My future SSc-ILD treatment regimen

Mild and/or slowly progressive disease
Nintedanib + mycophenolate mofetil

Extensive and/or rapidly progressive disease
For early, rapidly progressive disease with evidence of systemic inflammation – tocilizumab.
For other cases, rituximab or cyclophosphamide + nintedanib + mycophenolate mofetil.

Not all of these treatments are licensed for use in SSc-ILD.

Figure 3. Future treatment regimen of Toby M. Maher for SSc-ILD patients. SSc-ILD, systemic sclerosis-associated interstitial lung disease. Adapted from Maher TM. 2021.[7]

Based on these clinical data, Prof. Toby M. Maher explained his future SSc-ILD treatment regimen (**Figure 3**).[7] For patients with milder and/or slowly progressive disease, treatment options include nintedanib plus MMF while for patients with early, rapidly progressive disease with evidence of systemic inflammation, tocilizumab may be used. In other cases of extensive and/or rapidly progressive disease, nintedanib can be added as a combination therapy to rituximab or cyclophosphamide.

No pharmacological therapy is an option for a subset of SSc-ILD patients, but a close follow-up is required (**Figure 2**).[5] Those with early, stable or mild disease should be followed up regularly and in case of ILD progression, treatment should be initiated.

Due to the heterogeneous and variable course of ILD in SSc, it is important that patients are appropriately monitored after diagnosis. A post hoc analysis of prospectively collected patient data from the EUSTAR database demonstrated that 27% of SSc-ILD patients showed moderate or significant progression of ILD during any 12-month period, while about 2/3 of patients experienced progression at any time over the mean 5-year follow-up.[36] In both untreated and treated patients, multiple methods should be used to determine disease progression. These include changes in the extent of fibrosis or pattern on HRCT, changes in pulmonary function tests (FVC and DLCO absolute values or FVC decline), changes in exercise-induced oxygen desaturation and worsening of clinical symptoms.[5] However, according to the current recommendation, the decision to use HRCT should be based on a combination of the disease state and the speed of progression, as the overuse of HRCT should be avoided to reduce unnecessary radiation exposure.

Patients with evidence of disease progression or those with an inadequate response to treatment should be considered for treatment escalation, either by increasing the dose or by selecting an alternative therapy (**Figure 2**).[5] In case MMF and cyclophosphamide are not appropriate, nintedanib or rituximab could be a treatment option. Autologous hemopoietic stem cell transplant or lung transplant should be considered for selected patients with SSc-ILD. Furthermore, if nintedanib is not appropriate, MMF or cyclophosphamide are recommended. When monotherapies are not applicable, combination therapy with nintedanib and MMF should be considered.

Baseline dyspnea does not impact the efficacy of nintedanib in slowing the decline in lung function

In the randomized, double-blind, placebo-controlled, phase III SENSCIS trial, 52-week treatment with Ofev® (nintedanib) versus placebo was associated with a significantly lower rate of decline in lung function measured in FVC in patients with SSc-ILD (relative reduction: 44%; p=0.04).[34] At EULAR 2021, Dr Elizabeth R. Volkmann presented results of an analysis that aimed to compare baseline characteristics, the rate of decline in FVC and the effect of nintedanib in patients with and without dyspnea at baseline in SENSCIS.[9]

This trial enrolled adult SSc patients with an onset of the first non-Raynaud's symptom within 7 years before screening and fibrotic ILD affecting at least 10% of the lungs.[34] Patients also had to have an FVC that was at least 40% of the predicted value and a DLCO of 30–89% of the predicted value. Overall, 576 patients underwent 1:1 randomization to receive either nintedanib (150 mg orally twice daily) (n=288) or placebo (n=288), for up to 100 weeks.

In the present analysis, 70% of patients reported dyspnea at baseline and 30% did not.[9] Baseline demographics and clinical characteristics were generally balanced between these two subgroups, although patients with dyspnea had lower mean FVC % predicted (71.0% vs 76.5% without dyspnea), lower mean DLCO % predicted (50.9% vs 58.3%) and numerically greater mean extent of fibrotic ILD on HRCT (37.7% vs 31.6%).

In the placebo group, the rate of decline in FVC over 52 weeks was similar for patients with and without dyspnea at baseline (**Figure 4**).[9] Among patients without symptoms of breathlessness, the effect of nintedanib on reducing the rate of decline in FVC was numerically more pronounced than in patients with symptoms (difference: 79.8 mL/year vs 25.7 mL/year), although no statistically significant heterogeneity was observed between the subgroups (p=0.20). Results further indicated no statistical difference between the subgroups by dyspnea and the treatment effect of nintedanib on the absolute or relative decline in FVC >5% and >10% predicted.

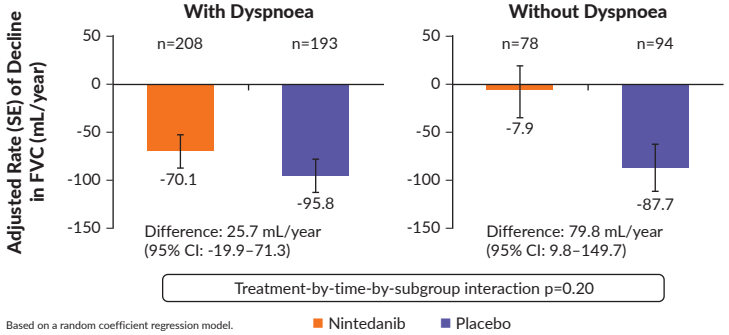

Figure 4. Adjusted rate of decline in forced vital capacity (FVC) over 52 weeks in subgroups by baseline dyspnea. SE, standard error. Adapted from Volkmann et al. 2021.[9]

CONCLUSIONS

- Screening, detecting and classifying ILD at the time of SSc diagnosis allows for early initiation of appropriate treatment[25], which has become possible with the advent of new therapeutic options, including nintedanib as one of the first approved antifibrotic treatments for SSc-ILD[8,34,35].
- Treatment options include nintedanib, mycophenolate mofetil (MMF) or cyclophosphamide as monotherapies for treatment initiation, or nintedanib in combination with mycophenolate mofetil (MMF) for treatment escalation.[6,7]
- An analysis of the SENSCIS trial data showed that the effect of nintedanib on reducing the rate of decline in FVC was nonsignificant numerically more pronounced in patients without dyspnea versus with dyspnea, suggesting that the presence of dyspnea alone should not be used to determine the timing of nintedanib initiation in SSc-ILD.[9]

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Abbreviated Professional Information Ofev® (nintedanib)

Ofev®: Nintedanib esylate (tyrosine kinase inhibitor). I: To treat idiopathic pulmonary fibrosis (IPF) *, chronic fibrosing interstitial lung diseases (ILD) with a progressive phenotype, and systemic sclerosis associated interstitial lung disease (SSc-ILD). D: Recommended dose: 150 mg 2x/day, 12 hours apart. CI: Pregnancy, hypersensitivity to nintedanib or any of the excipients, peanut, soya. Precautions: Use is not recommended in hepatic impairment associated with Child Pugh B, C. Child Pugh A: recommended dose 100 mg 2x/day. Cases of non-serious and serious drug-induced liver injury, in some cases with fatal outcome, have been observed. Hepatic transaminase and bilirubin levels should be monitored regularly during the first three months and thereafter. Dose reduction to 100 mg 2x/day if diarrhea, nausea, vomiting does not improve despite therapy, or if transaminase increases above three times upper limit of normal. Discontinue treatment in case of signs or symptoms of liver injury or if transaminase increases above five times upper limit of normal. Diarrhea and vomiting can lead to dehydration and electrolyte disturbances. Cases of renal impairment or renal failure, in some cases with fatal outcome, have been reported. Patients exhibiting risk factors for renal impairment should be monitored and their therapy adjusted. Therapy adjustment in case of renal impairment. Caution should be taken in the case of anticoagulant therapy, increased cardiovascular risk, hypertension, a history of aneurysms, arterial thromboembolic events, venous thromboembolism, and wound healing disorders. Cases of serious and fatal bleeding, gastrointestinal perforations and ischemic colitis, including fatal cases, have been reported. Caution should be taken in the case of recent abdominal surgery, perforation of a hollow organ, history of peptic ulcers, diverticulosis, or use of corticosteroids or NSAIDs. Discontinue treatment in cases of gastrointestinal perforation or ischemic colitis. Treatment should potentially be discontinued in case of symptoms of acute myocardial ischemia. P: Do not use during pregnancy, pause breast-feeding. Adequate contraception. UE: IPF: very common: diarrhea, nausea, abdominal pain, increased liver enzymes. Common: loss of appetite, weight loss, vomiting, bleeding (hematochezia, nosebleed, bruising; events with fatal outcome: gastrointestinal, intracranial, pulmonary bleeding, DIC), increases in liver enzymes (ALT, AST, GGT), rash, headaches. Uncommon: hypertension (incl. hypertensive crisis and hypertensive cardiomyopathy), thrombocytopenia, increase in AP, hyperbilirubinemia, drug-induced liver injury, pancreatitis, gastrointestinal perforation, colitis, pruritus, alopecia, proteinuria. Chronic fibrosing ILD: very common: diarrhea, nausea, abdominal pain, vomiting, increased liver enzymes, increased ALT, loss of appetite. Common: weight loss, headaches, hypertension, bleeding, increased AST, GGT, AP, drug-induced liver injury, rash. Uncommon: thrombocytopenia, pancreatitis, colitis, hyperbilirubinemia, pruritus, alopecia, proteinuria. SSc-ILD: very common: diarrhea, nausea, abdominal pain, vomiting, increased liver enzymes. Common: loss of appetite, weight loss, headaches, hypertension, bleeding, increased liver enzymes (ALT, AST, GGT, AP). Uncommon: thrombocytopenia, colitis, drug-induced liver injury, rash, pruritis, renal failure. IA: Potent P-gp inhibitors (ketoconazole, erythromycin) may increase exposure to nintedanib. Potent P-gp inducers (rifampicin, carbamazepine, phenytoin, St. John's Wort) may decrease exposure to nintedanib. Nintedanib exposure decreased on pirfenidone, nintedanib did not affect pirfenidone exposure. Use of bosentan did not alter the PK of nintedanib. Nintedanib should be taken with food. P: Capsules of 100 mg and 150 mg: 60. List B. *Reimbursable. Date of revision of the text: April 2021; full information for healthcare professionals at www.swissmedicinfo.ch. Boehringer Ingelheim (Schweiz) GmbH, Hochbergerstrasse 60B, PO Box, 4002 Basel.

SC-CH-00618

Understanding and Influencing the Disease Trajectory of **Rheumatoid Arthritis**

■ Many risk factors can lead to loss of tolerance and inflammation in rheumatoid arthritis (RA). Examining these risk factors and applying targeted therapies early may influence the disease trajectory of RA. At EULAR 2021, during the industry satellite symposium sponsored by Bristol Myers Squibb, Prof. Claire Daien from the University Hospital of Montpellier, France, talked about the microbiome's influence on the initiation of autoimmunity[1], while Prof. Andrew Cope from the Centre for Rheumatic Diseases, King's College London, UK, discussed the clinical potential of interventions in the at-risk RA state[2]. Finally, Prof. Hans U. Scherer, Leiden University Medical Centre, the Netherlands, highlighted the impact of targeted therapies early in RA development.[3]

RA involves a complex interplay between genotype and environmental factors. Along with many other human autoimmune diseases, RA is under strong genetic control by class II human leukocyte antigen (HLA) allele combinations.[4] The link between RA and *HLA-DRB1* locus has been confirmed in patients who are positive for rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA).[5–7] In particular, the **SHARED EPITOPE,** a five amino acid sequence motif encoded by *HLA-DRB1* alleles, is strongly associated with RA susceptibility. RF and/or ACPAs may develop years before the onset of clinical arthritis, suggesting that autoimmunity may be triggered at sites other than joints in patients with RA.[8] There is increasing evidence that the microbiome influences the development of autoimmunity and specific clinical bacterial signatures are associated with the autoantibody-positive disease.[6,9]

Microbiome's possible influence on the initiation of autoimmunity

The human microbiota consists of trillions of symbiotic microbial cells, primarily bacteria in the gut; and the human microbiome consists of the genes these cells harbor.[10,11] Estimates of the number of genes of the microbiome are reported 150 times the number of genes in the human genome. Similarly, the diversity among the microbiome of individuals is immense in terms of genomic variation. Approximately one-third of fecal bacterial taxa are heritable, underlining the importance of host genetics[12], and data indicate that microbiota might be altered in individuals with genetic predisposition to RA before the onset of RA[13]. Importantly, over 90% of RA patients have the shared epitope.[14] In addition to genetic disposition, environmental factors such as diet, smoking, air pollution, or medication can impact the microbiome.[15,16]

In healthy subjects, there is a symbiotic balance between the microbiome and the host.[17] Dysbiosis may lead to a decrease of microbial diversity and a disruption of this balance, potentially resulting in an alteration of the gut permeability and systemic inflammation.[18] An example of such a disturbed balance is periodontitis, dysbiotic conditions characterized by an imbalance between subgingival communities and host immune response, which is more frequent in RA patients compared with healthy control.[19] This may be related to the role of *P. gingivalis* in inducing citrullination that may lead to the development of the new antigens.[20] Therefore, changes in the oral or gut microbiota may affect mucosal immunity and induce aberrant immune responses that affect joints in patients with RA.[7]

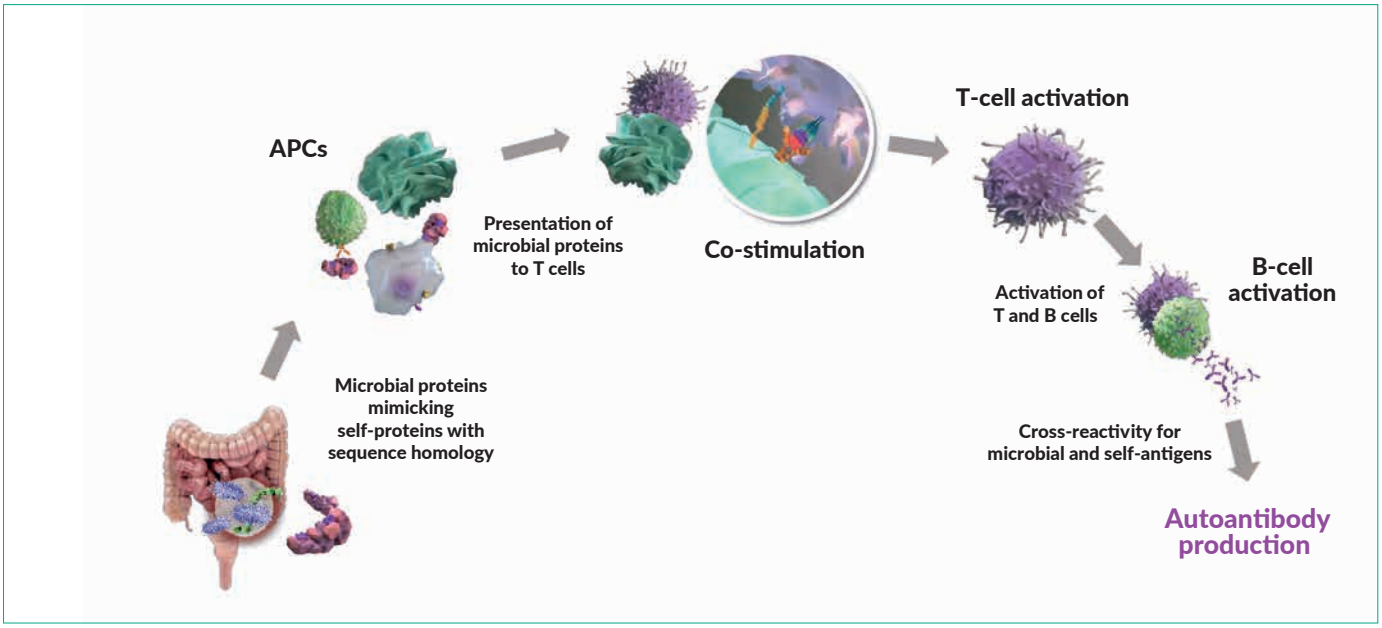

Figure 1. Gut microbiota may provoke autoantibody production through molecular mimicry. APCs, antigen-presenting cells. Adapted from Daien C. 2021.[1]

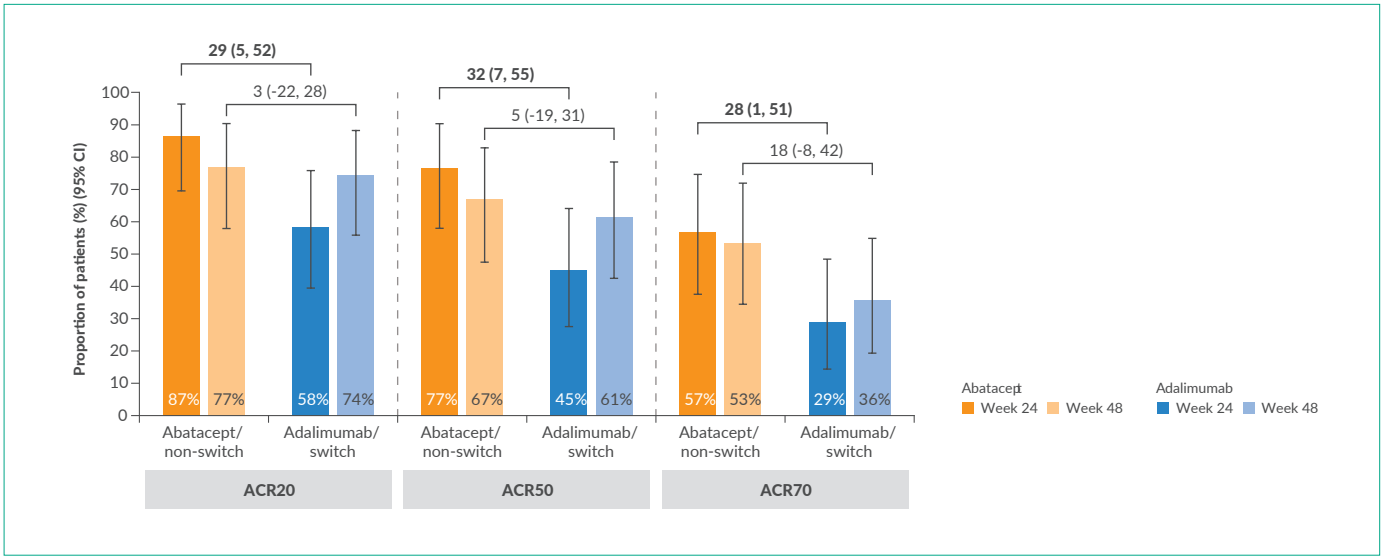

Figure 2. Early AMPLE: Proportions of patients with ACR responses in the shared epitope-positive (SE+) subpopulation. Numbers represent an estimate of difference (95% CI). SE, shared epitope. ACR20/50/70=20/50/70% improvement in ACR criteria. Adapted from Rigby et al. 2020.[48]

Several studies indicate that microbiota might influence the immune system on a cellular level. T cell epitope mimicry between microbial pathogens and self-proteins might induce or exacerbate autoimmune disease.[7] T cells activated by microbial peptides at the mucosal surface may then migrate to inflamed joints and cross-react with homologous self-antigens or induce the production of anti-microbiota antibodies that have a cross-reactivity for homologous self-antigens (**Figure 1**).[7,21] Another way the gut microbiota might promote loss of tolerance is by causing an expansion of autoreactive pro-inflammatory T helper (Th) 17 cells by stimulating their development, their migration to the lungs and joints and their support of ACPA glycosylation, further enhancing inflammation and autoimmunity.[22–24]

Lung dysbiosis may contribute to inflammation and pathology in the lung. Environmental exposures, such as smoking or pollution, might be associated with changes in the lung microbiome[15] and might initiate increased expression of citrullinated proteins leading to loss of tolerance and RA development.

The improvement of dysbiosis and RA disease is intertwined. In fact, emerging evidence suggests that reducing dysbiosis alleviates RA burden[25,26] and treating RA reduces dysbiosis[27]. Microbiota profiles may also predict responses to certain disease-modifying anti-rheumatic drugs (DMARDs), highlighting the need for a better understanding of the microbiome's role in the initiation of autoimmunity.[28]

The trajectory of the seropositive RA disease

RA is thought to develop as a consequence of complex interactions between different genetic and environmental factors.[29] Multiple factors indicate the presence of an at-risk state that could potentially lead to the development of clinical RA, such as genetic risk factors, autoantibody development and titers, increased levels of inflammatory markers and cytokines, arthralgia and subclinical bone erosions, changes in bone mineral density and cortical thickness.[6,30–32]

Patients with seropositive RA have an increased risk of certain comorbidities, higher frequencies of hospitalizations and durable medical equipment usage.[33] Ongoing and published trials have been examining the possibility of altering the trajectory of disease development and probing the biomarker profiles at these key stages of the disease, to reduce the burden on patients.[34–36]

Abatacept interrupts multiple pathogenic actions in RA

Patients with ACPA-positive disease have a less favorable prognosis than those with ACPA-negative disease[6] and the presence of ACPA is a factor of poor prognosis of RA[37]. Antibodies may be present years before the onset of the disease.[8] Abatacept inhibits pathogenic T cell-B cell interaction by blocking T cell co-stimulation. It is thought that this mode of action contributes to reducing ACPA titers, as well as cytokine release, osteitis and erosion progression.[38–46]

Several ongoing studies are assessing the efficacy of biologic DMARDs in patients with early RA. The phase IV NORD-STAR trial investigated the benefits and safety of three biological drugs with different modes of action, all given in combination with methotrexate, versus active conventional treatment (ACT) in treatment-naïve patients with rheumatoid arthritis.[47] At 24 weeks, a higher clinical disease activity index (CDAI) remission rate was observed for abatacept (delta 9.4% with ACT as reference) and certolizumab pegol (delta 3.9% with ACT as reference) versus ACT but not for tocilizumab (delta -0.6% with ACT as reference) versus ACT.[47] The group treated with abatacept had the fewest discontinuations, which contributed to its higher remission rate.[47] The number of patients who stopped treatment early was lowest for those receiving abatacept (11/204), compared with 20/200 patients in the ACT arm, 23/203 in the certolizumab pegol arm and 22/188 in the tocilizumab arm.[47] These results emphasize the importance of tolerability in the evaluation of drug efficacy.[47]

Further studies investigated the benefit of abatacept in biomarker-defined patients with early RA. The exploratory head-to-head Early AMPLE study assessed the clinical efficacy of abatacept versus adalimumab in ACPA-positive and RF-positive patients who were biologic treatment-naïve.[48] Overall, 80 patients were randomized to receive weekly oral methotrexate plus either subcutaneous (SC) abatacept (125 mg weekly) (n=40) or adalimumab (40 mg every 2 weeks) (n=40) for 24 weeks (single-blind period).[48] Following a 6-week washout period, adalimumab-treated patients changed to open-label SC abatacept (switch group), whilst abatacept-treated patients continued treatment in an open-label manner (non-switch group) for another 24 weeks.[48] Numerically greater efficacy responses (ACR20/50/70) were observed with abatacept versus adalimumab in the 24-week single-blind period, and the 24-week ACR20/50/70 responses were sustained through week 48 (78%, 63%, and 50%) in the abatacept non-switch group. In the switch group (from adalimumab to abatacept), efficacy responses generally improved over time to week 48.[48]

Interestingly, when assessing patient responses by the presence of the shared epitope, abatacept was also associated with numerically higher clinical response rates compared with adalimumab in the single-blind period (week 24), and responses were maintained until week 48, with ACR20/50/70 responses being 77%, 67%, and 53%, respectively (**Figure 2**).[48] The study also demonstrated that switching to abatacept improves remission status.[48] At week 48, a similar proportion of patients achieved clinical remission according to Disease Activity Score-28 (DAS28)-CRP with abatacept versus those from the switch group (48% vs 50%), with stronger responses observed in the non-switch versus switch shared epitope- positive patients (47% vs 42%).[48] These preliminary results suggest that abatacept response in seropositive patients with RA may be linked to the shared epitope.[48] The findings should be interpreted with caution due to a small sample size, and larger studies are warranted.

Over the course of more than a decade of RA patients being treated, abatacept showed a favorable safety profile in early RA patients.[49,50] A long-term safety analysis also found that the rate of serious infections among abatacept-treated patients decreased between 6 months and 24 months of treatment.[51]

CONCLUSIONS

- The microbiome can provoke the generation of modified autoantigens that may trigger inflammation and loss of tolerance in individuals at risk, leading to the development of rheumatoid arthritis (RA).[52]
- The RA disease trajectory passes from loss of tolerance to an at-risk state, which may be identified via serological and imaging biomarkers.[31]
- Abatacept may be beneficial to at-risk subjects, especially biomarker-defined patients, early in their disease trajectory, as suggested by trial results in early RA.[47,48]

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Effectiveness of IL-6 Receptor Inhibitor in Rheumatoid Arthritis

Patients with rheumatoid arthritis (RA) who have received multiple biologics or targeted therapies over time tend to have more refractory and more severe disease, which may lead to a worse clinical response to treatment. At EULAR 2021, Dr Stefano Fiore presented results from a study that used data from the ACR RISE registry to assess whether disease severity was greater in those who received sarilumab, an anti-interleukin (IL)-6 receptor monoclonal antibody, shortly after its Food and Drug Administration (FDA) approval than in subsequent time periods.[1] In addition, this study aimed to evaluate the effectiveness of sarilumab in populations with various degrees of disease severity.

Stefano Fiore, MD
Sanofi
Bridgewater, NJ, USA

Real-world US experience with sarilumab from the ACR RISE registry

In this analysis, patients with RA who initiated sarilumab treatment between 2017 and 2020 were divided into Cohort 1 (2017, year of the FDA approval) and the calendar year-based Cohorts 2–4 (2018–2020). Between-cohort comparisons were made using a chi-square test for categorical variables and a nonparametric test for continuous variables.

Sarilumab effectiveness was assessed using 3 cohorts assembled based on progressively restrictive criteria: Active Disease cohort (Clinical Disease Activity Index [CDAI] >10 or Routine Assessment of Patient Index Data 3 [RAPID3] >6 and C-reactive protein ≥8 mg/L), TARGET Eligibility cohort (patients who satisfied enrolment criteria for TARGET) and TARGET Baseline cohort (patients from TARGET Eligibility cohort with characteristics weighted to match those from the TARGET trial baseline). In all 3 effectiveness cohorts, mean changes in CDAI and RAPID3 at 6 and 12 months post-initiation of sarilumab were evaluated using a model adjusted for baseline score, age, sex, race, calendar year and seropositivity.

The greatest clinical improvement with sarilumab observed in the cohort with the highest baseline CDAI

A total of 2,949 RA patients initiated sarilumab treatment in the period 2017–2020.[1] The 4 yearly cohorts were relatively similar in terms of demographics and most clinical characteristics. However, patients receiving sarilumab shortly after FDA approval (Cohort 1) had more ambulatory visits, a greater number of previously used non-tumor necrosis factor inhibitor (TNFi) biologics (particularly tocilizumab) and a higher comorbidity burden, as compared with Cohorts 2–4. In addition, they were more likely to be current users of glucocorticoids or opioids than sarilumab initiators in the subsequent 3 years.

Data further indicated that mean baseline CDAI varied substantially by cohort, with the greatest mean baseline CDAI score (42 units) in the TARGET Baseline cohort, compared with the other two cohorts (24 units both).[1] Among the 3 effectiveness cohorts, both the crude and adjusted (**Figure 1A**) improvements in CDAI at 6 and 12 months were greater in the TARGET Baseline versus Active Disease and TARGET Eligibility cohorts. Similar trends were observed in terms of crude and adjusted (**Figure 1B**) improvement in RAPID3.

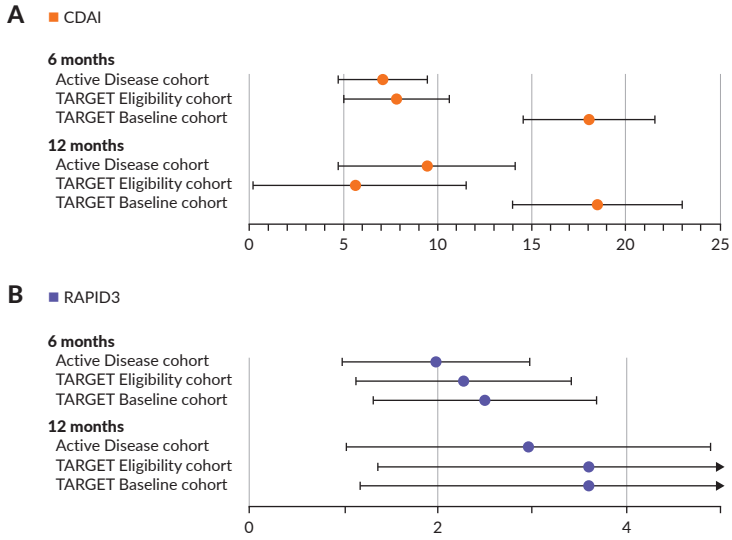

Figure 1. Adjusted improvement in (A) CDAI and (B) RAPID3, by cohort. CDAI, Clinical Disease Activity Index; RAPID 3, Routine Assessment of Patient Index Data 3. Adapted from Fiore et al. 2021.[1]

CONCLUSIONS

- This real-world cohort showed modest evidence for channeling of patients with greater severity of rheumatoid arthritis (RA) and greater prior exposure to non-tumor necrosis factor inhibitor (TNFi) biologics to sarilumab shortly after its FDA approval.[1]
- Clinical improvement with sarilumab was observed across all cohorts, with the greatest clinical improvement in the cohort with the highest baseline CDAI score that most closely resembled patients with an inadequate response to TNF inhibitors enrolled in a phase III trial.

[1] Fiore S et al. Disease severity and outcomes among patients with rheumatoid arthritis who receive a newly approved biologic: real-world US experience with sarilumab from the ACR RISE registry. EULAR 2021 Virtual Congress; 2–5 June 2021. Poster presentation POS0638.

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1 **KEVZARA®** Fachinformation, Stand Februar 2021; www.swissmedicinfo.ch; **2** Genovese MC *et al.* Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol* 2015; 67(6): 1424–37; **3** Fleischmann R *et al.* Sarilumab and non-biologic disease-modifying antirheumatic drugs in patients with active RA and inadequate response or intolerance to TNF inhibitors. *Arthritis Rheumatol* 2017; 69: 277–90; **4** Burmester GR *et al.* Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis* 2017; 76: 840–47.

Kevzara®. W: Sarilumab. **I:** In Kombination mit Methotrexat (MTX) zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei erwachsenen Patienten, die auf eines oder mehrere DMARDs unzureichend angesprochen oder diese nicht vertragen haben. Kann als Monotherapie indiziert sein, wenn MTX nicht vertragen wird oder ungeeignet ist. **D:** 200 mg 1 Mal alle 2 Wochen subkutan. Bei Auftreten einer Neutropenie, Thrombozytopenie oder erhöhter Leberenzymwerte Reduzierung auf 150 mg 1 Mal alle 2 Wochen. **KI:** Überempfindlichkeit gegen den Wirkstoff oder einen der Hilfsstoffe. Schwere aktive Infektionen (z. B. aktive Tuberkulose, Sepsis, schwere opportunistische Infektionen). **VM:** Bei Auftreten von Anzeichen einer Infektion engmaschig überwachen. Bei Infektion in der aktiven Phase einschliesslich lokaler Infektionen nicht mit Kevzara behandeln. Bei bestimmten Faktoren (s. FI) vor Behandlung Nutzen-Risiko abwägen. Bei Neuauftreten einer Infektion für immunsupprimierte Patienten angemessene Diagnostik durchführen und entsprechende mikrobielle Therapie einleiten und engmaschig überwachen. Vor Behandlungsbeginn auf Risikofaktoren für Tuberkulose und auf Vorliegen einer latenten Infektion untersuchen. Gegebenenfalls Tuberkulosetherapie erwägen. Unter Behandlung von Immunsuppressiva biologischen Ursprungs wurde eine Reaktivierung von Virusinfektionen beobachtet. Eine Behandlung mit Kevzara ist mit erhöhter Häufigkeit einer verringerten absoluten Neutrophilenzahl (ANC) und mit einer Abnahme der Thrombozytenzahl assoziiert. Die verringerte ANC ging jedoch nicht mit einem häufigeren Auftreten von Infektionen (einschliesslich schwerwiegender) und eine verringerte Thrombozytenzahl nicht mit Blutungsereignissen einher. Eine Behandlung bei geringer Neutrophilenzahl (2×10^9/l) und mit einer Thrombozytenzahl < 150×10^3/µl wird nicht empfohlen. Die Behandlung mit Kevzara ist mit einer erhöhten Häufigkeit eines Anstiegs der Transaminasewerte assoziiert. Der Anstieg ist vorübergehend und geht nicht mit klinisch manifesten Leberläsionen einher. Häufigerer und ausgeprägterer Anstieg der Transaminasewerte bei Kombination mit potenziell hepatotoxischen Arzneimitteln. Eine Behandlung wird bei erhöhten Transaminasewerten (ALAT oder ASAT > 1,5 x ULN) nicht empfohlen. Die Lipidkonzentration kann bei Patienten mit chronischer Entzündung herabgesetzt sein. Die Behandlung mit Kevzara ist mit der Erhöhung von Lipidparametern wie LDL- und HDL-Cholesterin sowie Triglyzeride assoziiert. Vorsicht bei erhöhtem Risiko für gastrointestinale Perforation. Es wurden Fälle von gastrointestinaler Perforation beobachtet. Eine Behandlung mit Immunsuppressiva kann das Risiko für maligne Erkrankungen erhöhen. Überempfindlichkeitsreaktionen sind möglich. Am häufigsten Ausschlag an der Injektionsstelle, Hautrötung und Urtikaria. Behandlung bei aktiver Lebererkrankung oder Leberinsuffizienz nicht empfohlen. Die gleichzeitige Anwendung von Lebendimpfstoffen und Kevzara ist zu vermeiden, da die klinische Sicherheit nicht nachgewiesen ist. Patient aufmerksam auf Symptome überwachen, die auf das Auftreten einer demyelisierenden Erkrankung des zentralen Nervensystems hindeuten. **IA:** Zytokine und Zytokinmodulatoren können die Expression und Aktivität bestimmter Cytochrom-P450(CYP)-Enzyme beeinflussen. Somit können sie bei gleichzeitiger Gabe von Arzneimitteln, die Substrate dieser Enzyme sind, potenziell deren Pharmakokinetik verändern. Wird eine Behandlung mit Kevzara eingeleitet oder abgesetzt bei Patienten mit gleichzeitiger Gabe von CYP-Substraten, ist die Wirkung (z. B. bei Warfarin) bzw. die Wirkstoffkonzentration (z. B. bei Theophyllin) therapeutisch zu überwachen und die individuelle Arzneimitteldosierung bei Bedarf anzupassen. Besondere Vorsicht bei gleichzeitiger Gabe mit einem Substrat von CYP3A4 (z. B. orale Kontrazeptiva oder Statine). Gleichzeitige Anwendung mit Lebendimpfstofffen vermeiden. **NW:** Neutropenie, Thrombozytopenie, Infektionen (auch schwere Infektionen), erhöhte Lipid- und Transaminasewerte, Reaktionen an der Injektionsstelle. **P:** 2 Fertigspritzen a 150 mg und 200 mg Injektionslösung. 2 Fertigpens a 150 mg und 200 mg Injektionslösung. **AK:** B. **Zul-Inh.:** sanofi-aventis (schweiz) ag, 1214 Vernier/GE. **Stand Info.:** Februar 2021. Weitere Informationen entnehmen Sie bitte der Fachinformation unter www.swissmedicinfo.ch.

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SANOFI GENZYME

Real-World Data on IL-6 Receptor Inhibition in Elderly Patients with **Rheumatoid Arthritis**

■ Due to increasing life expectancy, there is a large proportion of elderly patients with rheumatoid arthritis (RA), underlining the need for effective RA treatments for this subset of patients. Pivotal clinical trials have demonstrated the efficacy of tocilizumab in patients with RA[1–6]; however, data on the effectiveness of tocilizumab in the elderly are limited. ICHIBAN was a large, observational study that followed patients with RA treated with tocilizumab in clinical practice for up to 2 years.[7] At EULAR 2021, Prof. Christof Specker presented the analysis assessing the safety and effectiveness of long-term tocilizumab treatment according to patient baseline age.[8]

Christof Specker, MD, PhD
Kliniken Essen-Mitte, Clinic of Rheumatology and Clinical Immunology
Essen, Germany

Long-term tocilizumab is effective with an acceptable safety profile in elderly RA patients

This non-interventional, prospective study enrolled adult patients with active moderate to severe RA in rheumatology clinics and practices in Germany.[7] Patients were treated with tocilizumab according to the local label. The safety analysis set comprised all eligible patients who received at least one dose of tocilizumab, including patients with tocilizumab exposure prior to the study. The effectiveness set consisted of all patients from the safety analyses set who had no prior tocilizumab therapy. Patient-reported outcomes (PROs) were assessed using the visual analog scale (VAS).

Similar rates of adverse events across three age groups

At data cutoff, 3,164 patients received at least one dose of tocilizumab.[8] The mean age was 55.5 years and about 80% of patients were female. At baseline, 29.2% of patients were <50 years old, 47.3% were 50–65 years old and 23.5% of patients were

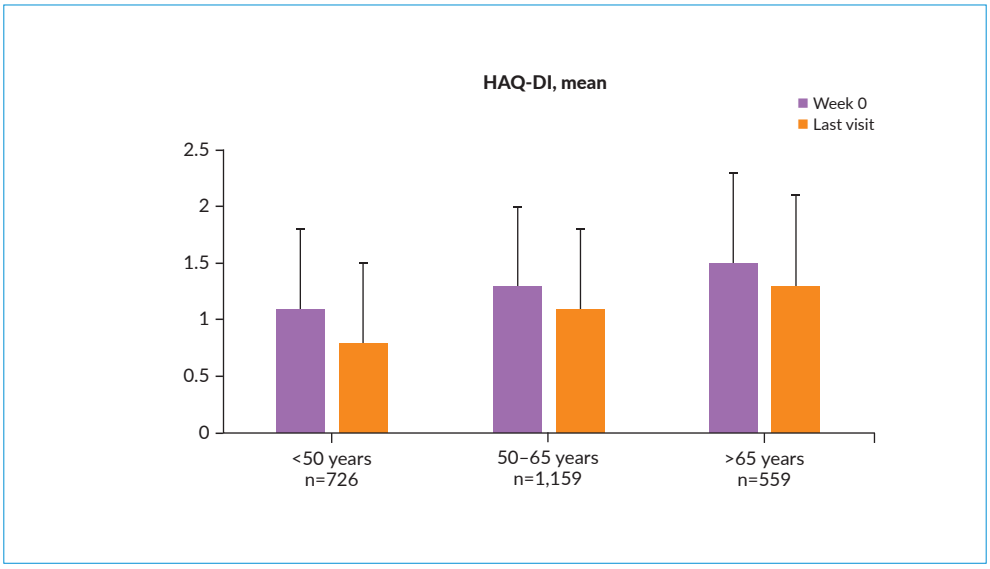
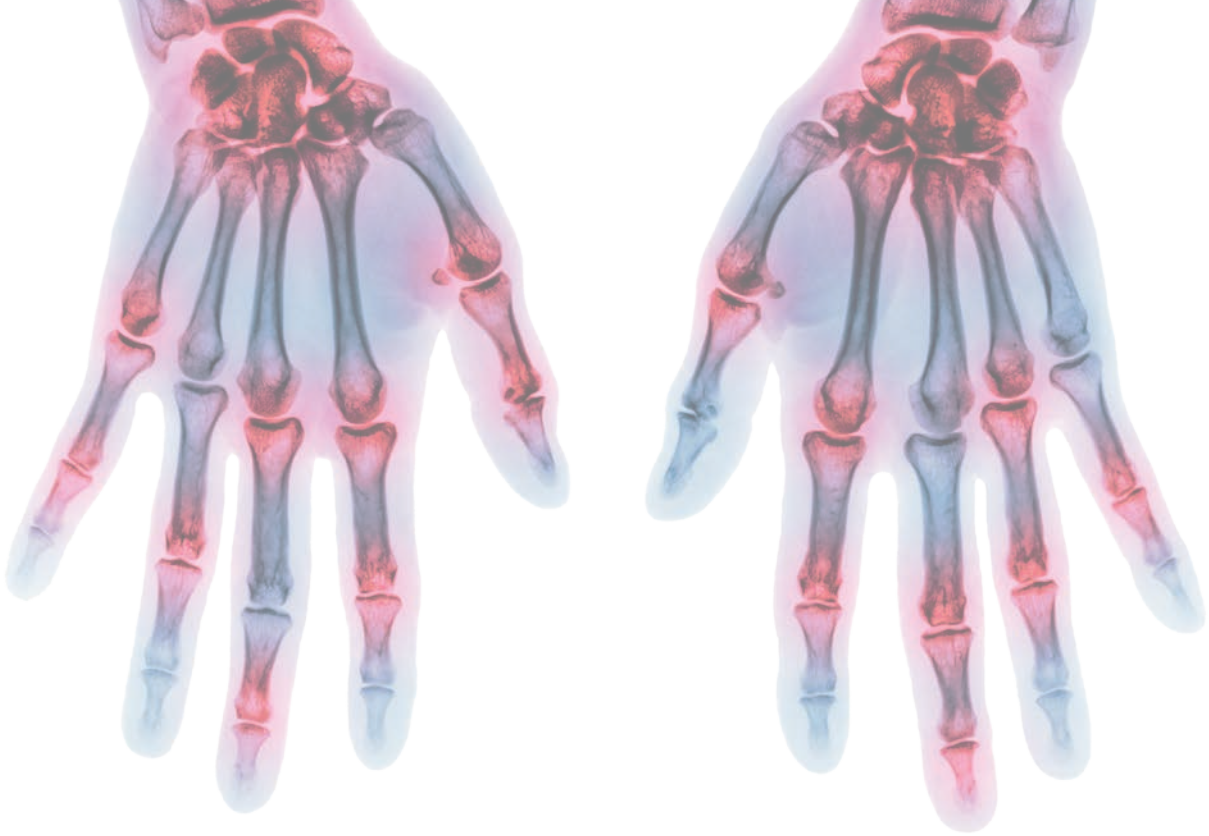


Figure 1. Mean (SD) Health Assessment Questionnaire Disease Index (HAQ-DI) score across three age subgroups. SD, standard deviation. Adapted from Specker et al. 2021.[8]



>65 years old. Compared with younger patients, a greater proportion of those >65 years old had comorbidities such as hypertension, anemia, renal insufficiency, osteoporosis, diabetes and coronary heart disease. In addition, older patients had the highest baseline disease activity according to Disease Activity Score-28 erythrocyte sedimentation rate (DAS28-ESR) and Clinical Disease Activity Index (CDAI).

Regarding safety, there was no difference in the rates of treatment-related adverse events (AEs) across the age subgroups (<50 years: 22.3%; 50–65 years: 21.9%; >65 years: 22.2%).[8] More patients aged >65 years and 50–65 years experienced serious AEs (SAEs) than patients <50 years (20.2% and 14.4% vs 11.5%). Similarly, slightly more patients >65 years old experienced serious infections (4.8%) than younger patients (<50 years: 3.2% and 50–65 years: 3.1%). However, the discontinuation rate of tocilizumab due to AEs was comparable across three subgroups, ranging from 7.0% in the <50-years-old subgroup to 7.8% in the >65-years and 9.6% in the 50–65-years subgroups.

Similar benefits to disease activity in patients aged >65 years

In the efficacy population (n=2,902), the proportion of patients achieving DAS28-ESR remission at least once during the treatment period was higher among patients aged <50 years, as compared with patients aged 50–65 and >65 years (65.4% vs 59.8% and 59.5%). However, at the last visit, patients >65 years old had numerically greater improvements in the mean DAS28-ESR score from baseline versus those aged 50–65 or >65 years.

Results further showed that patients <50 years old had the best physical functioning at baseline and the greatest reduction in Health Assessment Questionnaire Disease Index (HAQ-DI) score (**Figure 1**). All age groups had similar improvements from baseline in PROs such as fatigue, strength of pain and sleep disturbances.

CONCLUSIONS

- The discontinuation rate due to AEs was similar across three age subgroups, although more patients aged >65 years experienced infections.[8]
- Patients >65 years old had similar benefits in terms of disease activity and patient-reported outcomes (PROs) when compared with younger patients.

1 Smolen JS et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008; 371(9617): 987–97.
2 Yazici Y et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012; 71(2): 198–205.
3 Jones G et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010; 69(1): 88–96.
4 Genovese MC et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008; 58(10): 2968–80.
5 Emery P et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008; 67(11): 1516–23.
6 Burmester GR et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis. 2014; 73(1): 69–74.
7 Specker C et al. ICHIBAN, a non-interventional study evaluating tocilizumab long-term effectiveness and safety in patients with active rheumatoid arthritis. Clin Exp Rheumatol. 2021; 39(2): 319–28.
8 Specker C et al. Tocilizumab is safe and effective in elderly patients with rheumatoid arthritis.EULAR 2021 Virtual Congress; 2–5 June 2021. Poster presentation POS0615.

Long-Term Benefit with JAK1 Inhibitor in Patients with **Rheumatoid Arthritis**

■ In the phase III SELECT-COMPARE trial, the highly selective Janus kinase (JAK) 1 inhibitor upadacitinib demonstrated significant improvements in the signs and symptoms of rheumatoid arthritis (RA) at weeks 12 and 72 when administered on a background of methotrexate (MTX), as compared with adalimumab plus MTX.[1,2] At EULAR 2021, Prof. Roy M. Fleischmann presented 3-year follow-up results of SELECT-COMPARE.[3]

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University of Texas Southwestern
Medical Center
Dallas, TX, USA

SELECT-COMPARE: Upadacitinib plus MTX continued to surpass adalimumab plus MTX across 3 years

Overall, 1,629 patients treated with background methotrexate were randomized 2:2:1 to receive either upadacitinib 15 mg once daily (n=651), placebo (n=651) or adalimumab 40 mg every other week (n=327), for up to 48 weeks.[1] Between weeks 14 and 26, patients with <20% improvement in the tender joint count (TJC), swollen joint count (SJC) or Clinical Disease Activity Index (CDAI) >10 were rescued without washout from placebo or adalimumab to upadacitinib, or from upadacitinib to adalimumab. Patients randomized to placebo who were not rescued were switched to upadacitinib at week 26. Patients who completed the 48-week double-blind period entered the open-label long-term extension (LTE) period for up to 5 years.

Significant improvement with upadacitinib versus adalimumab maintained

Between weeks 14 and 26, a total of 252 patients (39%) were rescued from upadacitinib to adalimumab, while 159 (49%) were rescued from adalimumab to upadacitinib; all placebo patients were crossed over to upadacitinib.[3] In the long-term extension, a higher proportion of patients randomized to upadacitinib completed 3 years of treatment without rescue compared with those randomized to adalimumab (47% vs 36%).

At week 156, upadacitinib versus adalimumab was associated with improved clinical responses.[3] Patients treated with upadacitinib plus methotrexate (MTX) showed increased rates of American College of Rheumatology (ACR) responses, as compared with patients receiving adalimumab plus MTX. Furthermore, a higher proportion of patients treated with upadacitinib than adalimumab achieved low disease activity or remission at 3 years based on CDAI, as well as Disease Activity Score (DAS) 28 C-reactive protein (CRP) scores of ≤3.2 or <2.6 (**Figure 1**).

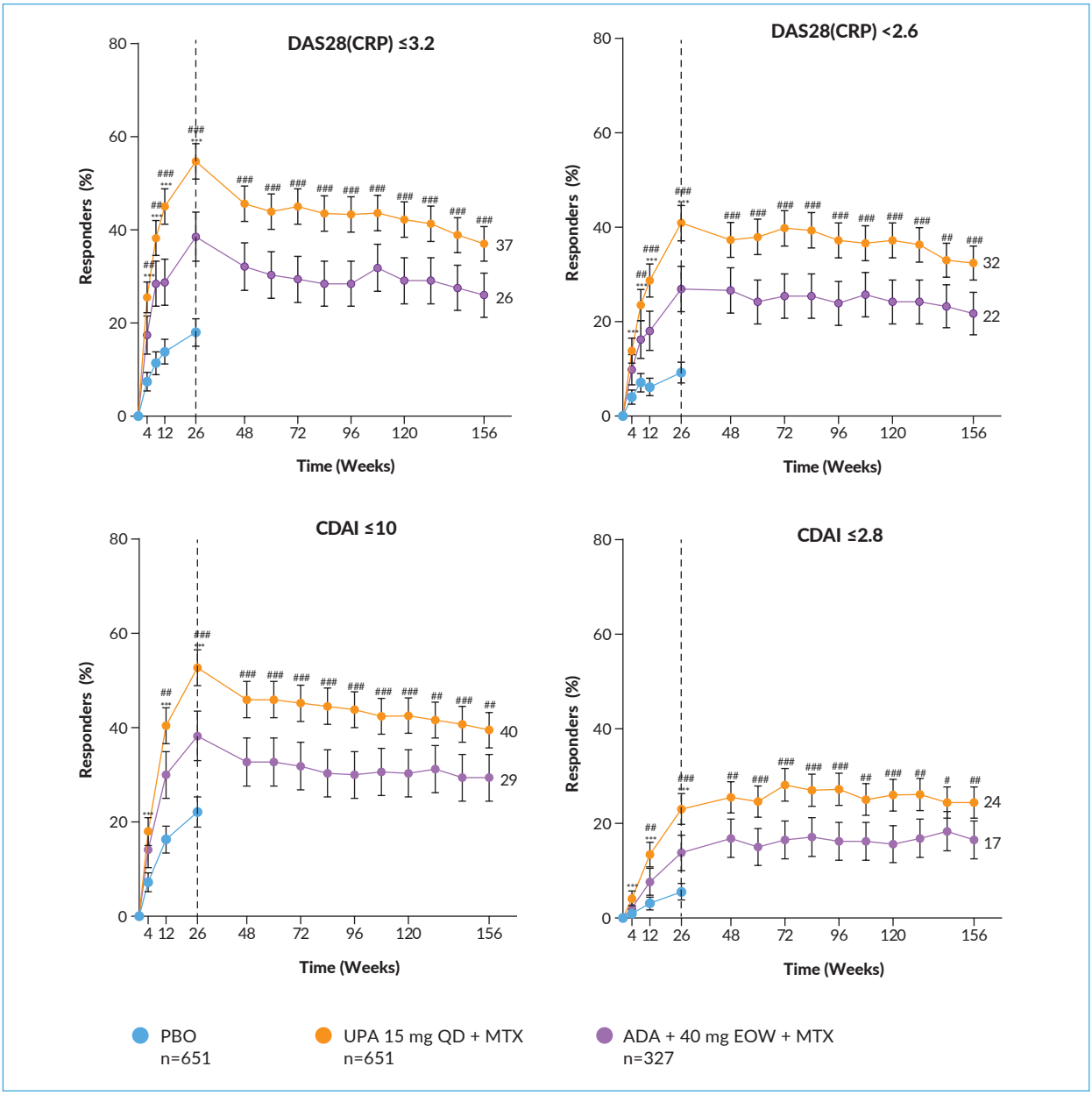

Figure 1. Clinical response rates upon treatment with upadacitinib, placebo and adalimumab. *p<0.05, **p<0.01, ***p<0.001 for UPA plus MTX; #p<0.05, ##p<0.01, ###p<0.001 for UPA vs ADA. ADA, adalimumab; CDAI, Clinical Disease Activity Index; CRP, c-reactive protein; DAS28, Disease Activity Score 28; EOW, every other week; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib. Adapted from Fleischmann et al. 2021.[3]

Regarding patient-reported outcomes, upadacitinib demonstrated significant improvements in the Health Assessment Questionnaire Disability Index (HAQ-DI) (mean change from baseline; upadacitinib: -0.75 vs adalimumab: -0.60; p<0.01) and reduction in pain (-39.8 vs -31.2; p<0.001).

Safety profile consistent with previous reports

Upadacitinib was generally well tolerated as assessed by rates of serious adverse events (AEs), AEs leading to study drug discontinuation and events of special interest (AESI), such as serious and opportunistic infections, malignancies, adjudicated major adverse cardiac events or venous thromboembolism.[3] As observed in previous analyses, the frequency of AESIs was generally comparable between the upadacitinib and the adalimumab arm, except for herpes zoster, lymphopenia, hepatic disorder and creatine phosphokinase elevation, which were more common in the upadacitinib arm.

CONCLUSIONS

- Over 3 years, upadacitinib plus methotrexate (MTX) continued to demonstrate higher levels of clinical response compared with adalimumab plus MTX, in patients with rheumatoid arthritis.[3]
- The safety profile of upadacitinib was consistent with the previously established phase III safety analysis.

[1] Fleischmann RM et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. Arthritis Rheumatol. 2019; 71(11): 1788–800.

[2] Fleischmann RM et al. Long-term safety and effectiveness of upadacitinib or adalimumab in patients with rheumatoid arthritis: results at 72 weeks from the SELECT-COMPARE study. EULAR 2020 E-Congress; 3–6 June 2020.. Poster presentation THU0201.

[3] Fleischmann RM et al. Long-Term Safety and Efficacy of Upadacitinib or Adalimumab in Patients with Rheumatoid Arthritis: Results at 3 years From the SELECT-COMPARE Study (EULAR). EULAR 2021 Virtual Congress; 2–5 June 2021. Oral presentation POS0087.

IL-23 Inhibitor Improves Symptoms of Active Psoriatic Arthritis in Patients with **Inadequate Response to TNF Inhibition**

■ Guselkumab, an anti-interleukin (IL)-23 antibody, showed significant improvements in joint and skin symptoms versus placebo in patients with active psoriatic arthritis (PsA) in the phase III DISCOVER-1 and DISCOVER-2 trials.[1,2] At EULAR 2021, Prof. Laura Coates presented results from the phase IIIb COSMOS study that evaluated the efficacy and safety of guselkumab in patients with active PsA with inadequate response or intolerance to tumor necrosis factor (TNF) inhibition.[3]

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University of Oxford
Oxford, United Kingdom

Guselkumab improves outcomes in patients with active PsA and prior TNF-inhibition treatment failure

This double-blind, placebo-controlled trial enrolled 285 adults with active PsA and ≥3 swollen and ≥3 tender joints for ≥6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria at screening and had failed one or two TNF inhibitors.[3] Patients were randomized in a 2:1 ratio to receive either subcutaneous guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks (n=189) or placebo (n=96). Methotrexate, sulfasalazine, hydroxychloroquine or leflunomide were permitted background medications. At week 16, placebo-treated patients who met early escape (EE) criteria, defined as <5% improvement in both tender and swollen joint counts, could cross over to receive guselkumab. At week 24, all patients in the placebo group were switched to guselkumab. The primary efficacy endpoint was the proportion of patients who achieved an American College of Rheumatology (ACR) 20 response at week 24.

Guselkumab achieved a significantly higher ACR20 rate at week 24

The primary endpoint was met, with a significantly higher ACR20 response rate achieved with guselkumab versus placebo at week 24 (44.4% vs 19.8%; p<0.001) (**Figure 1**).[3] Results of the "EE-correction" sensitivity analysis, which included those incorrectly routed to early escape, were consistent with the primary analysis, showing an ACR20 response rate of 48.1%. Treatment effects

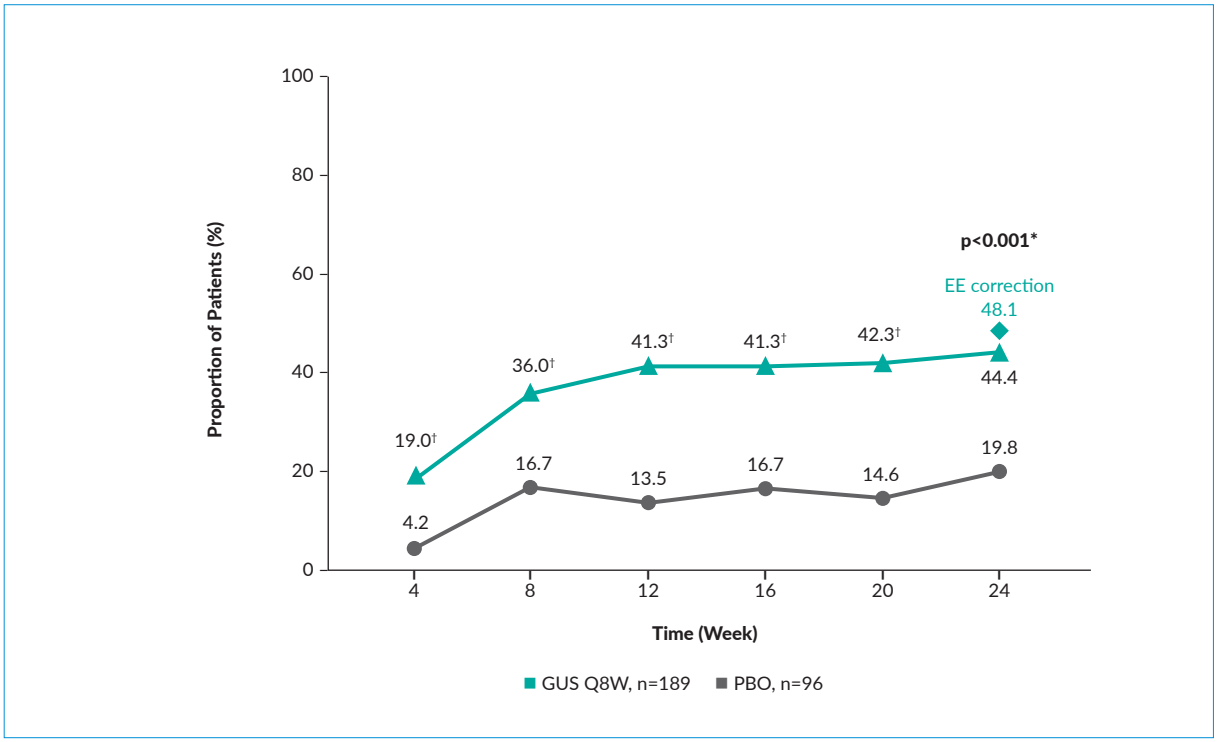

Figure 1. ACR20 response rates in the COSMOS study for guselkumab versus placebo. *p<0.001 adjusted for multiplicity; †p<0.001 nominal. ACR, American College of Rheumatology; EE, early escape; GUS, guselkumab; PBO, placebo; Q8W, every 8 weeks. Adapted from Coates et al. 2021.[3]

with guselkumab were seen as early as week 4 and the proportion of patients who achieved an ACR20 response increased through week 48. The benefit of guselkumab versus placebo for ACR20 at week 24 was consistent across subgroups defined by baseline patient and disease characteristics, and prior and concomitant medications.[3]

At week 24, guselkumab versus placebo also demonstrated significant improvements in all major secondary endpoints, including physical function (mean change from baseline in Health Assessment Questionnaire-Disability Index [HAQ-DI]: -0.18 vs -0.01; p=0.003), health-related quality of life (short-form [SF] 36-item physical component score [PCS]: 3.51 vs -0.39; p<0.001), complete skin clearance (PASI 100: 33.8% vs 3.8%; p<0.001) and the more stringent joint response criteria of ACR50 (19.6% vs 5.2%; p=0.001).[3] In addition, higher rates of enthesitis (39.7% vs 18.8%) and dactylitis (55.6% vs 40.0%) resolution were seen at week 24 for guselkumab versus placebo, respectively. Further improvements by week 48 were observed across all secondary endpoints.

Guselkumab demonstrated a favorable benefit:risk profile

Through week 56, guselkumab demonstrated safety consistent with the established safety profile among psoriasis and PsA patients.[3] Rates of adverse events did not increase throughout the study. There were no cases of opportunistic infection, active tuberculosis, anaphylactic/serum sickness-like reaction, confirmed inflammatory bowel disease or deaths.

CONCLUSIONS

- In patients with active psoriatic arthritis and inadequate response to TNF inhibition, guselkumab demonstrated significantly higher American College of Rheumatology (ACR) 20 response rates versus placebo at week 24.[3]
- Guselkumab was also associated with significant improvements in physical function, health-related quality of life, complete skin clearance for patients with baseline psoriasis and ACR50.
- Guselkumab was well tolerated through week 56 of treatment, consistent with its established safety profile in psoriasis and PsA patients.

[1] Deodhar A et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020; 395(10230): 1115–25.
[2] Mease PJ et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020; 395(10230): 1126–36.
[3] Coates L et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who demonstrated inadequate response to tumor necrosis factor inhibition: Week 24 results of a phase 3b, randomized, controlled study. EULAR 2021 Virtual Congress; 2–5 June 2021. Oral presentation OP0230.

Treating **Psoriatic Arthritis** with a JAK Inhibitor

■ In the phase III SELECT-PsA 2 study, upadacitinib, an oral Janus kinase (JAK) inhibitor, demonstrated efficacy and acceptable safety profile at 24 weeks in patients with psoriatic arthritis (PsA) and prior inadequate response to ≥1 biologic disease-modifying antirheumatic drug (DMARD).[1] At EULAR 2021, Prof. Philip J. Mease presented updated results of the trial.[2]

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and University of Washington
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SELECT-PsA 2: 56-week update showed maintained efficacy of upadacitinib in PsA patients

In this study, 641 adult PsA patients were randomized 1:1:1 to receive either blinded treatment with upadacitinib (15 or 30 mg once daily) for 56 weeks or placebo, with a switch to either 15 mg or 30 mg upadacitinib at week 24.[1] Concomitant therapy with ≤2 non-biologic DMARDs was permitted but not required. Starting at week 36, patients with less than 20% improvement in tender and swollen joint counts at 2 consecutive visits discontinued the study drug. Efficacy endpoints included proportions of patients achieving 20%, 50% and 70% improvement in the American College of Rheumatology (ACR) criteria (ACR20/50/70) and minimal disease activity (MDA), as well as 75%, 90% and 100% improvement in the Psoriasis Area and Severity Index (PASI75/90/100) and resolution of dactylitis and enthesitis. Treatment-emergent adverse events (TEAEs) were summarized for events occurring up to 30 days after the last dose.

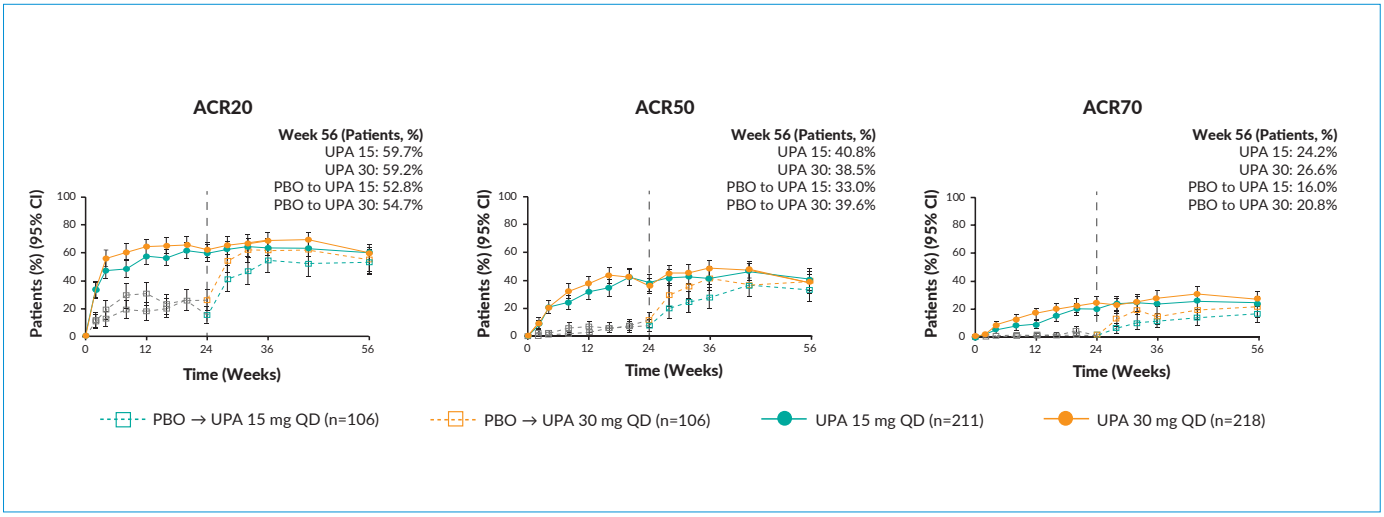
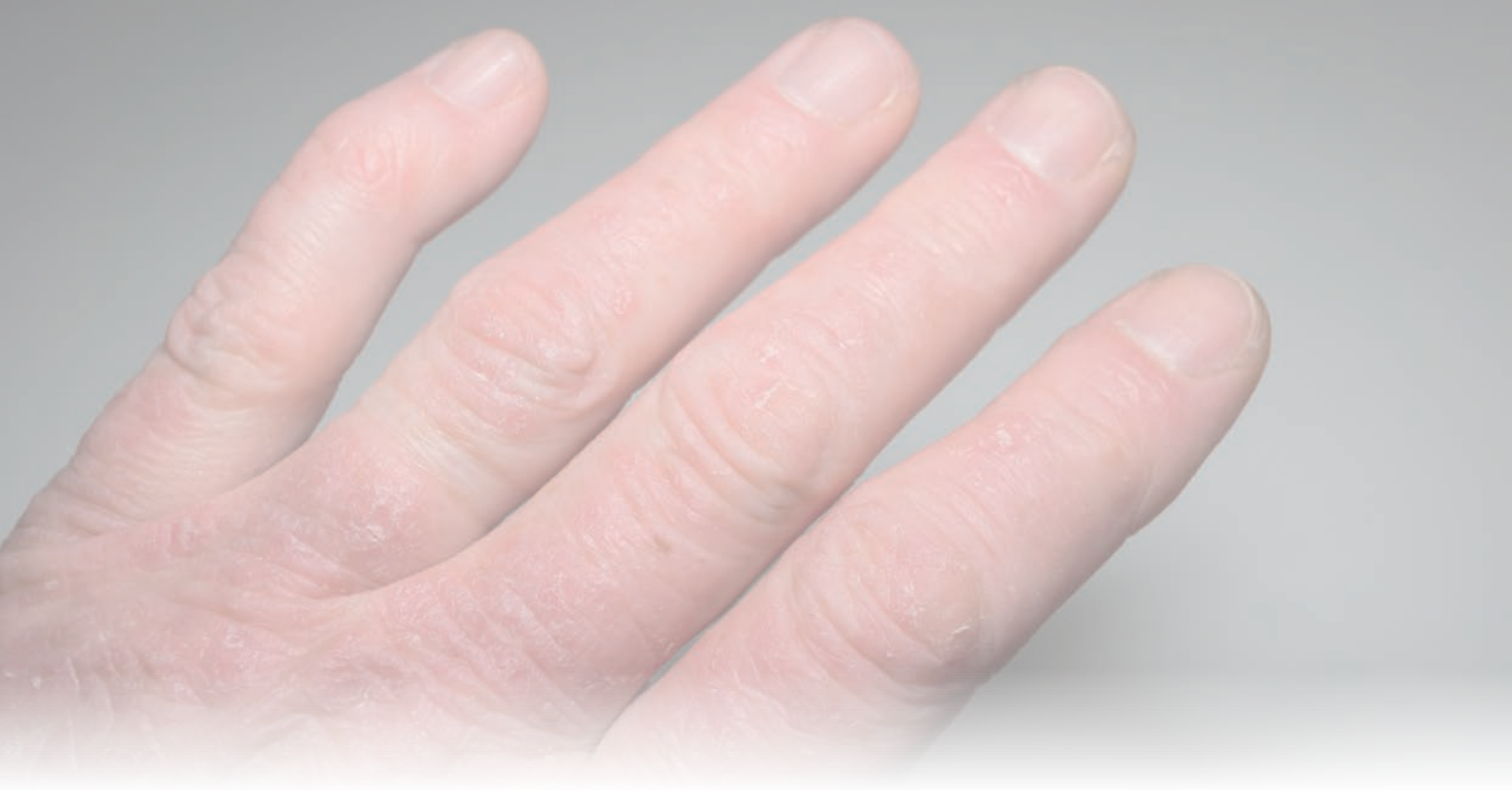


Figure 1. Clinical improvements upon treatment with upadacitinib based on ACR20/50/70. ACR, American College of Rheumatology; PBO, placebo; QD, daily; UPA, upadacitinib. Adapted from Mease et al. 2021.[2]



Upadacitinib maintains efficacy over 56 weeks

Overall, 74.7% of patients completed 56 weeks of treatment.[2] At data cutoff, the proportions of patients who achieved ACR20/50/70 were sustained through week 56 of treatment (**Figure 1**). Similarly, clinical improvements based on the proportion of patients achieving MDA, PASI75/90/100 and resolution of dactylitis and enthesitis were also maintained over 1 year. In patients with dactylitis at baseline, complete resolution of the symptoms was observed in 50.9% and 58.0% of patients treated with upadacitinib 15 mg and 30 mg, respectively, by week 56, while 42.9% and 42.8% of patients, respectively, with enthesitis as baseline experienced a complete resolution of enthesis. Through week 56, there were also improvements in several patient-reported outcomes (PROs) using as-observed (AO) data for patients who received upadacitinib at 15 mg and 30 mg doses from baseline.

Consistent safety profile

The safety profile of upadacitinib was consistent with previous reports.[1,3] In this analysis, rates of treatment-emergent adverse events (AEs) were generally lower with the lower dose of upadacitinib.[2] There was a dose-dependent increase in exposure-adjusted event rates of serious infections, herpes zoster, hepatic disorders, hematologic lab-related AEs and creatine phosphokinase (CPK) elevations; however no difference was observed for exposure-adjusted incidence rates of major adverse cardiovascular events, venous thromboembolic events or malignancies. No case of adjudicated gastrointestinal perforation was observed, and clinically significant laboratory abnormalities were infrequent.

CONCLUSIONS

- In patients with psoriatic arthritis (PsA) and prior inadequate response to ≥1 biologic disease-modifying antirheumatic drug (DMARD), upadacitinib demonstrated sustained efficacy over 56 weeks, with no new safety signals.[2]
- Improvements observed with upadacitinib 15 mg were similar to those with the 30 mg dose over 56 weeks.
- Patients who switched from placebo to upadacitinib at week 24 experienced similar clinical improvements as those who were initially randomized to upadacitinib.

[1] Mease PJ et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis. 2020; 80(3): 312–20.
[2] Mease PJ et al. Upadacitinib in patients with psoriatic arthritis refractory to biologic disease-modifying antirheumatic drugs: 56-week data from the phase 3 SELECT-PsA 2 study. EULAR 2021 Virtual Congress; 2–5 June 2021. Poster presentation POS0196.
[3] Cohen SB et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis. 2020: 80(3): 304–11.

Treatment of Severe **Lupus Nephritis**

■ Lupus nephritis is the most common severe manifestation of systemic lupus erythematosus (SLE), which presents with proteinuria, hematuria and impaired kidney function.[1] The goal of treatment for active lupus nephritis is nephron preservation by reversing the inflammatory process and achieving inactive disease.[2] At EULAR 2021, Prof. Frédéric A. Houssiau discussed therapeutic approaches that may improve long-term renal outcomes in patients with lupus nephritis.[3]

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Switch from sequential to combination therapy reduces deterioration in renal function

Management of patients with active lupus nephritis comprises sequential therapy consisting of initial induction therapy with potent immunosuppressive medications, such as mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide, both combined with glucocorticoids, followed by long-term maintenance therapy with MMF or azathioprine, with no or low-dose glucocorticoids.[4] Available therapies induce complete clinical renal response (CRR) rates in only 20–30% of patients at 6–12 months, with a relapse rate of 20–25% at 3–5 years.[5–7] The prognosis of lupus nephritis may be improved with a switch from the current sequential to combination therapy.[3]

Clinical trials on combination therapies in lupus nephritis

Several combination therapies for the treatment of patients with lupus nephritis have been investigated in phase II and III clinical trials. The double-blind, randomized, phase III AURORA 1 trial evaluated voclosporin, a calcineurin inhibitor, versus placebo, added to MMF and rapidly tapered low-dose steroids.[8] At week 52, voclosporin was associated with clinically and statistically superior CRR rate versus placebo (41% vs 23%; p<0.0001), with a safety profile balanced between the two treatment groups.

Belimumab, a recombinant human IgG1λ monoclonal antibody that inhibits B-cell activating factor, was the first biologic approved for the treatment of systemic lupus erythematosus (SLE), based on the results from two phase III clinical trials, BLISS-52 and BLISS-76.[9–11] Belimumab has been further investigated in the recent phase III BLISS-LN trial, which enrolled 448 patients with active lupus nephritis who were randomized 1:1 to receive either belimumab or placebo.[12] Randomization was stratified according to induction regimen (cyclophosphamide vs MMF) and race. At week 104, significantly more patients treated with belimumab versus placebo had a primary

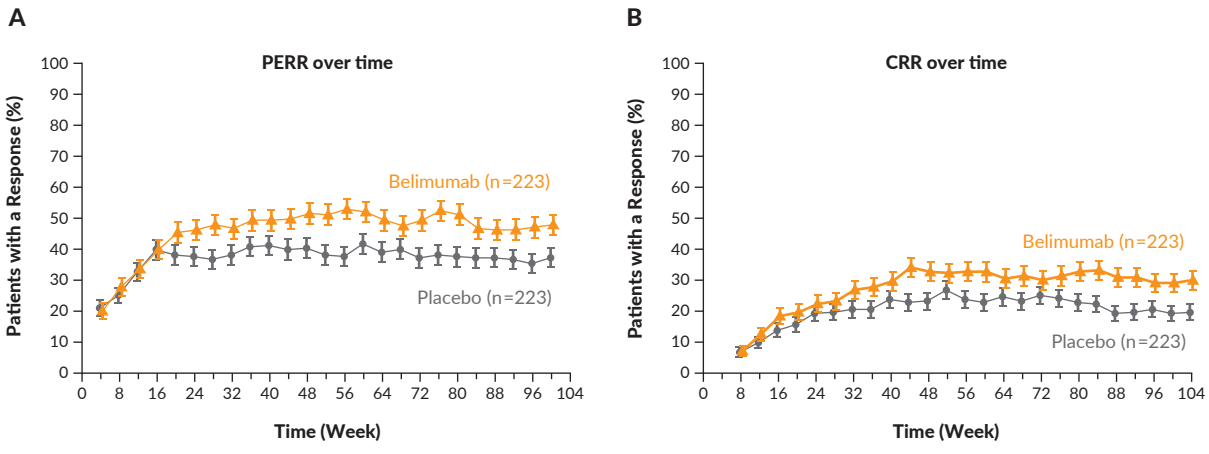
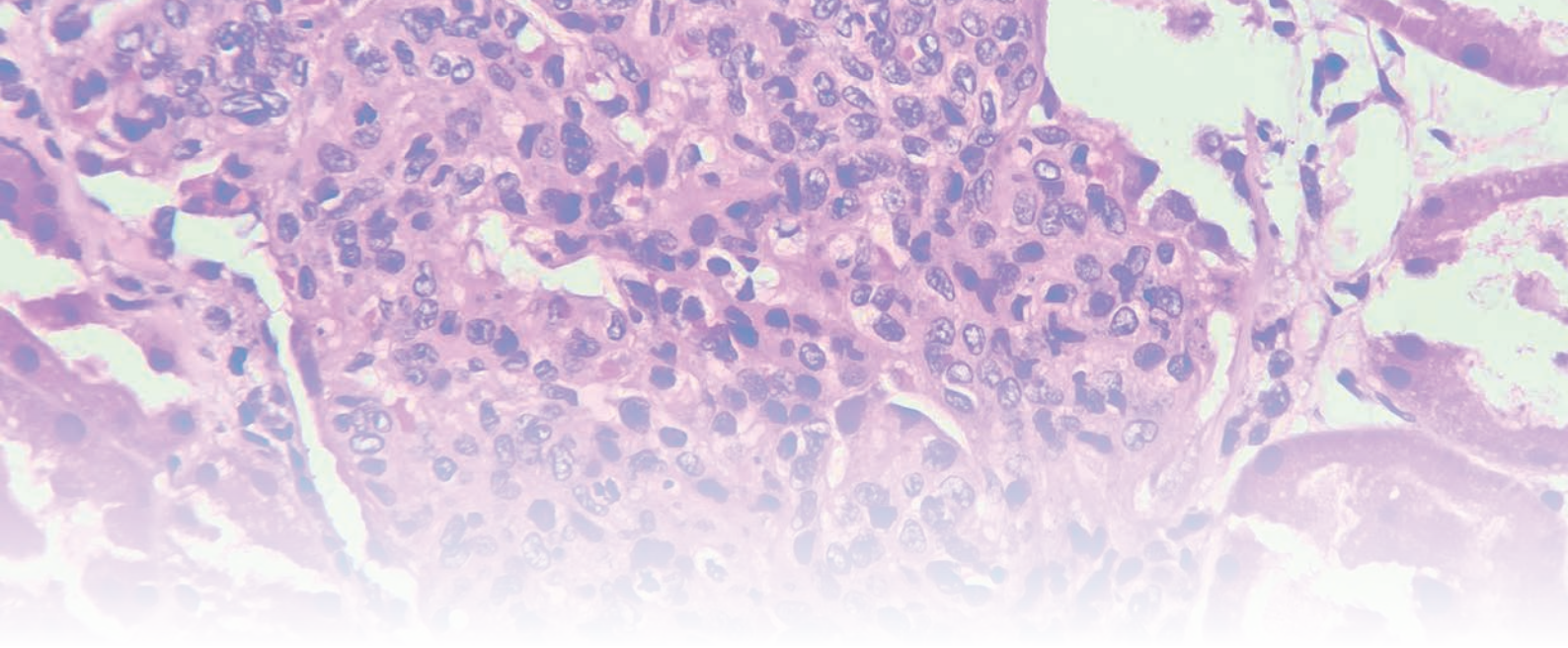


Figure 1. Renal responses over time in the modified intention-to-treat population.. CRR, complete renal response; PERR, primary efficacy renal responses. Adapted from Furie et al. 2020.[12]



efficacy renal response (43.0% vs 32.3%; odds ratio [OR]: 1.6 [95% CI: 1.0–2.3]; p=0.031) (**Figure 1A**) and a CRR (30.0% vs. 19.7%; OR: 1.7 [95% CI: 1.1–2.7]; p=0.017) (**Figure 1B**). The risk of a renal-related event or death was also lower in patients receiving belimumab than those receiving placebo (HR: 0.51 [95% CI: 0.34–0.77]; p=0.001). A subgroup analysis further showed that belimumab versus placebo was associated with improved primary efficacy renal response at week 104, irrespective of induction therapy, while CRR at week 104 favored belimumab only in the MMF subgroup, with no between-group difference in the cyclophosphamide subgroup. The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone.

The phase II, double-blind NOBILITY trial aimed to test the hypothesis that enhanced B-cell depletion with obinutuzumab, a type II anti-CD20 monoclonal antibody, will result in improved responses in proliferative lupus nephritis.[13] Overall, 125 patients with class III or IV lupus nephritis received obinutuzumab or placebo, with the standard of care. Data showed that obinutuzumab versus placebo achieved improved CRR rates at week 52 (35% vs 23%; p=0.115), week 76 (40% vs 18%; p=0.007) and week 104 (41% vs 23%; p=0.026), with fewer obinutuzumab-treated patients requiring a new rescue therapy through week 104.[13] Rates of serious adverse events, serious infections and deaths were comparable between the two treatment groups.

Recently, the phase II TULIP-LN study assessed anifrolumab, a fully human monoclonal antibody that binds to subunit 1 of the type I IFN receptor, versus placebo in patients with active proliferative lupus nephritis.[14] Patients were randomized 1:1:1 to anifrolumab basic regimen, intensified regimen or placebo, alongside standard therapy. Although the study did not meet the primary endpoint of the relative difference in change from baseline to week 52 in 24-hour urine protein-creatinine ratio (UPCR), the anifrolumab intensified regimen was associated with numeric improvements across clinical endpoints, including the CRR rate at week 52. Regarding safety, most adverse events were nonserious, mild, or moderate and did not lead to discontinuation.

The choice of treatment is based on various aspects such as the patients' extra-renal diseases, specific toxicity profile, drug availability and reimbursement criteria.[3] However, in order to choose the most appropriate treatment combination for an individual patient, highly valuable may be a tissue level analysis of the kidneys assessing the type of immune cell infiltrates, the number of antibody-secreting cells (ASC) in the tubular interstitial, global or single-cell ASC transcriptomics and a liquid biopsy for assessing ASC in urine.[15,16]

CONCLUSIONS

- A switch from sequential to combination therapy is warranted since the current standard of care does not meet the expectations of patients or physicians.[3]
- In the largest and longest lupus nephritis study, the phase III BLISS-LN trial, belimumab plus standard therapy was associated with an increased rate of complete renal response, as compared with standard therapy alone.[12]
- Tissue level analysis using innovative tools may help to identify the most appropriate combination therapy.[3]

[1] Hanly JG et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016; 55(2): 252–62.
[2] Chan TM. Treatment of severe lupus nephritis: the new horizon. Nat Rev Nephrol. 2015; 11(1): 46–61.
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[5] Houssiau FA. Management of Lupus Nephritis: An Update. J Am Soc Nephrol. 2004; 15(10): 2694–704.
[6] Houssiau FA et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: Lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum. 2004; 50(12): 3934–40.
[7] Houssiau FA, Ginzler EM. Current treatment of lupus nephritis. Lupus. 2008; 17(5): 426–30.
[8] Rovin BH et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021; 397(10289): 2070–80.
[9] Benlysta® (belimumab). Product information. Swissmedicinfo. [Accessed September 2021]. Available from: www.swissmedicinfo.ch.
[10] Navarra SV et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011; 377(9767): 721–31.
[11] Furie R et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011; 63(12): 3918–30.
[12] Furie R et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Eng J Med. 2020; 383(12): 1117–28.
[13] Rovin B et al. Two-Year Results from a Randomized, Controlled Study of Obinutuzumab for Proliferative Lupus Nephritis. ASN 2020; 22–25 October 2020. Oral presentation SU-OR31.
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[15] Pamfil C et al. Intrarenal activation of adaptive immune effectors is associated with tubular damage and impaired renal function in lupus nephritis. Ann Rheum Dis. 2018; 77(12): 1782–9.
[16] Crickx E et al. Molecular Signatures of Kidney Antibody-Secreting Cells in Lupus Patients With Active Nephritis Upon Immunosuppressive Therapy. Arthritis Rheumatol. 2021; 73(8): 1461–6.

Towards Reduction of Glucocorticoid Usage in Patients with **Giant Cell Arteritis**

■ Long-term glucocorticoid therapy is accompanied by numerous side effects. In two randomized controlled trials, tocilizumab, an anti-IL-6 receptor antibody, demonstrated a glucocorticoid-reducing effect of at least 50% in patients with giant cell arteritis.[1,2] At EULAR 2021, Dr Lisa Christ and Prof. Peter M. Villiger presented data of the proof-of-concept GUSTO study[3], which assessed the efficacy and safety of tocilizumab after ultra-short glucocorticoid therapy in patients with new-onset giant cell arteritis.[4]

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Bern, Switzerland

Peter M. Villiger, MD
Inselspital Bern
Bern, Switzerland

GUSTO: Tocilizumab after ultra-short glucocorticoid treatment achieved sustained remission in patients with newly diagnosed giant cell arteritis

This investigator-initiated, single-arm, single-center, open-label trial enrolled 18 patients older than 50 years with newly diagnosed giant cell arteritis who had C-reactive protein (CRP) levels >25 mg/l and previous glucocorticoid treatment for a maximum of 10 days at a maximum dose of 60 mg/day.[4] Patients received 500 mg methylprednisolone intravenously for 3 consecutive days. Thereafter, glucocorticoid treatment was discontinued and tocilizumab at a dose of 8 mg/kg was administered intravenously, followed by the subcutaneous administration of 162 mg tocilizumab weekly from day 10 until week 52. The primary endpoint was the proportion of patients who achieved remission within 31 days and were relapse-free until week 24. The secondary endpoint included the proportion of patients with complete relapse-free remission of disease at week 52. An interim analysis was performed after the first 12 patients reached the primary endpoint.

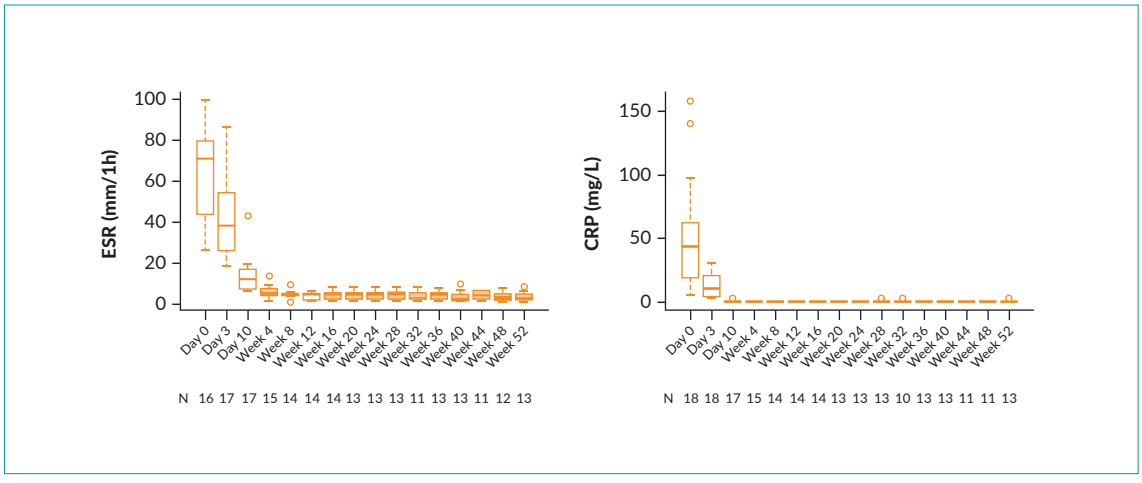

Figure 1. Development of laboratory parameters during treatment with tocilizumab. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Adapted from Christ et al. 2021.[4]

High remission and relapse-free rates by week 52

At baseline, the median age was 71 years, 12 patients were female and 11 patients had received prior glucocorticoid treatment.[4] A total of 15 patients (83%) showed cranial symptoms, while 13 (72%) had positive histopathology.

An interim analysis at week 24 showed that only 3 of 12 patients (25%) achieved the primary endpoint of remission within 31 days and had no disease relapse.[4] However, results further indicated that 11 of 12 patients were in remission after a mean of 10.6 weeks and that 10 of these patients were relapse-free. At a complete analysis at week 52, 14 patients achieved remission after a mean of 11.1 weeks; of these, 13 patients remained relapse-free up to week 52. Overall, 3 patients were non-responders, 2 of which had persistent cranial symptoms (including one with new-onset anterior ischaemic optic neuropathy), while the third patient had persistent polymyalgia rheumatica symptoms. The reduction of symptoms upon tocilizumab after ultra-short glucocorticoid was accompanied by decreased levels of inflammation markers (**Figure 1**) and thrombocytes, as well as an increase in hemoglobin level.

Altogether, 3 patients experienced a serious adverse event (AE), including diverticulitis, oral aphthous lesion and nausea.[4] Two patients discontinued the study due to an AE (hepatopathy and diverticulitis, respectively), one of them after induction of remission. In one patient, the tocilizumab application interval needed to be prolonged due to neutropenia.

CONCLUSIONS

- In the GUSTO trial, tocilizumab after ultra-short glucocorticoid therapy induced and maintained remission in patients with newly diagnosed giant cell arteritis.[4]
- As a proof-of-concept study, these data do not allow proposing clinical recommendations.

[1] Villiger PM et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016; 387(10031): 1921–7.
[2] Stone JH et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017; 377(15): 1494–5.
[3] Christ L et al. Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. Lancet Rheumat. 2021; 3(9): e619–26.
[4] Christ L et al. A proof-of-concept study to assess the efficacy of tocilizumab monotherapy after ultra-short glucocorticoid administration to treat giant cell arteritis - the GUSTO trial. EULAR 2021 Virtual Congress; 2–5 June 2021. Oral presentation OP0061.

TNF Inhibitor Exposure During Pregnancy in Patients with **Chronic Inflammatory Diseases**

In line with recent guidelines, women of reproductive age suffering from chronic inflammatory diseases (CID), such as rheumatoid arthritis (RA), axial spondyloarthritis (SpA), psoriatic arthritis (PsA) and Crohn's disease (CD), are increasingly being treated with tumor necrosis factor inhibitors (TNFi).[1] However, clinical trial data on the effect of TNFi on pregnancy outcomes are still limited. Certolizumab pegol, a PEGylated, Fc-free TNFi, has minimal to no active placental transfer from mother to infant during the third trimester.[2] At EULAR 2021, Dr Megan Clowse presented results from a study that aimed to assess pregnancy outcomes from the UCB Pharmacovigilance safety database from prospectively reported pregnancies exposed to certolizumab pegol.[3]

Megan Clowse, MD
Duke University Medical Center,
Division of Rheumatology and Immunology
Durham, NC, USA

No increased risk for adverse pregnancy outcomes or specific congenital malformations after exposure to certolizumab pegol during pregnancy

In this study, data on certolizumab pegol-exposed pregnancies were obtained from the UCB Pharmacovigilance safety database through November 2020.[3] Analysis was limited to prospectively reported cases with known pregnancy outcomes to avoid potential reporting bias associated with retrospective submissions. Confounding factors, such as specific CIDs, concomitant non-biologic medications and maternal infection, were evaluated using a multivariate stepwise regression model. Patients with missing information about the presence or absence of confounders were excluded from the model.

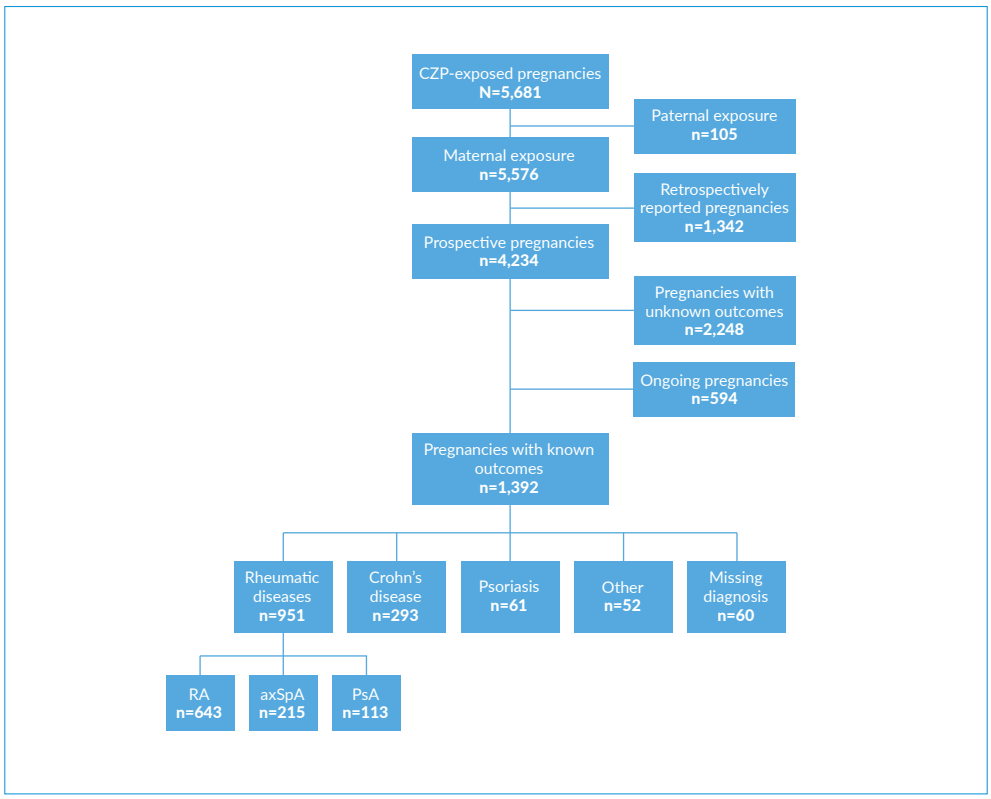

Figure 1. Reports of pregnancies exposed to certolizumab pegol in the UCB Pharmacovigilance safety database. Some patients may have had multiple indications for treatment with certolizumab pegol. axSpA, axial spondyloarthritis; CZP, certolizumab pegol; PsA, psoriatic arthritis; RA, rheumatoid arthritis. Adapted from Clowse et al. 2021.[3]

Concomitant corticosteroids increase the risk for preterm birth and low birth weight

There were 1,392 prospective pregnancies (1,425 fetuses) with maternal exposure to certolizumab pegol and known outcomes.[3] The main indications were rheumatic diseases (n=951) and CD (n=293) (**Figure 1**) and the mean baseline maternal age was 31.9 years. Altogether, 73.3% of pregnancies had at least first-trimester exposure to certolizumab pegol and 39.3% were exposed during all trimesters. At data cutoff, normal rates of live births (88.4%), abortions (miscarriages and terminations) (10.5%), stillbirths (0.8%) and ectopic pregnancies (0.4%) were reported. Preterm births occurred in 9.8% of live births and 8.0% of infants had low birth weight (<2.5 kg).

Congenital malformations were reported in 2.5% of fetuses and 2.4% of live-born infants; 2.1% of congenital malformations were major according to the Metropolitan Atlanta Congenital Defects Program criteria.[3] Adverse events observed in the newborns did not show any patterns of specific congenital malformations.

Data further showed that corticosteroid use was independently associated with increased likelihood of preterm birth (odds ratio [OR]: 2.1 [95% CI: 1.3–3.4]; p<0.005) and low birth weight (OR: 1.7 [95% CI: 1.0–2.9]; p<0.05), but decreased odds of abortion (OR: 0.5 [95% CI: 0.3–0.9]; p<0.05).[3] Increased probability of pregnancy loss was reported in women treated with concomitant non-steroidal anti-inflammatory drugs (NSAIDs) (OR: 2.2 [95% CI: 1.2–4.0]; p<0.05) .[3] and methotrexate/leflunomide (OR: 3.2 [95% CI: 1.7–6.2]; p<0.0005). Furthermore, maternal infections were indicated as a risk factor for preterm birth (OR: 1.9 [95% CI: 1.1–3.5]; p<0.05), while patients with a diagnosis of Crohn's disease were at increased risk of having an abortion (OR: 2.5 [95% CI: 1.5–4.1]; p=0.0005) and those with RA were at increased risk of low birth weight (OR: 1.9 [95% CI: 1.1–3.3]; p<0.05).

CONCLUSIONS

- Results from this large prospective analysis showed no increase in adverse pregnancy outcomes or specific congenital malformations in certolizumab pegol-exposed pregnancies, as compared with the general population.[3]
- This study confirmed the impact of specific chronic inflammatory diseases (CIDs), concomitant drugs or comorbidities on pregnancy outcomes.

[1] Sammaritano LR et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020; 72(4): 529–56.
[2] Mariette X et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018; 77(2): 228–33.
[3] Clowse M et al. Pharmacovigilance pregnancy data in a large population of patients with chronic inflammatory disease exposed to certolizumab pegol: pregnancy outcomes and confounders. EULAR 2021 Virtual Congress; 2–5 June 2021. Poster presentation POS0022.

TNF Inhibition in **Ankylosing Spondylitis**

■ The GO-ALIVE study demonstrated that golimumab, a tumor necrosis factor (TNF) inhibitor, significantly reduced the signs and symptoms of ankylosing spondylitis (AS) at week 28 in adult patients, with efficacy maintained across 1 year.[1,2] At EULAR 2021, Prof. Atul Deodhar presented results of a post hoc analysis evaluating golimumab in AS patients with early versus late disease through week 52.[3]

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Portland, OR, USA

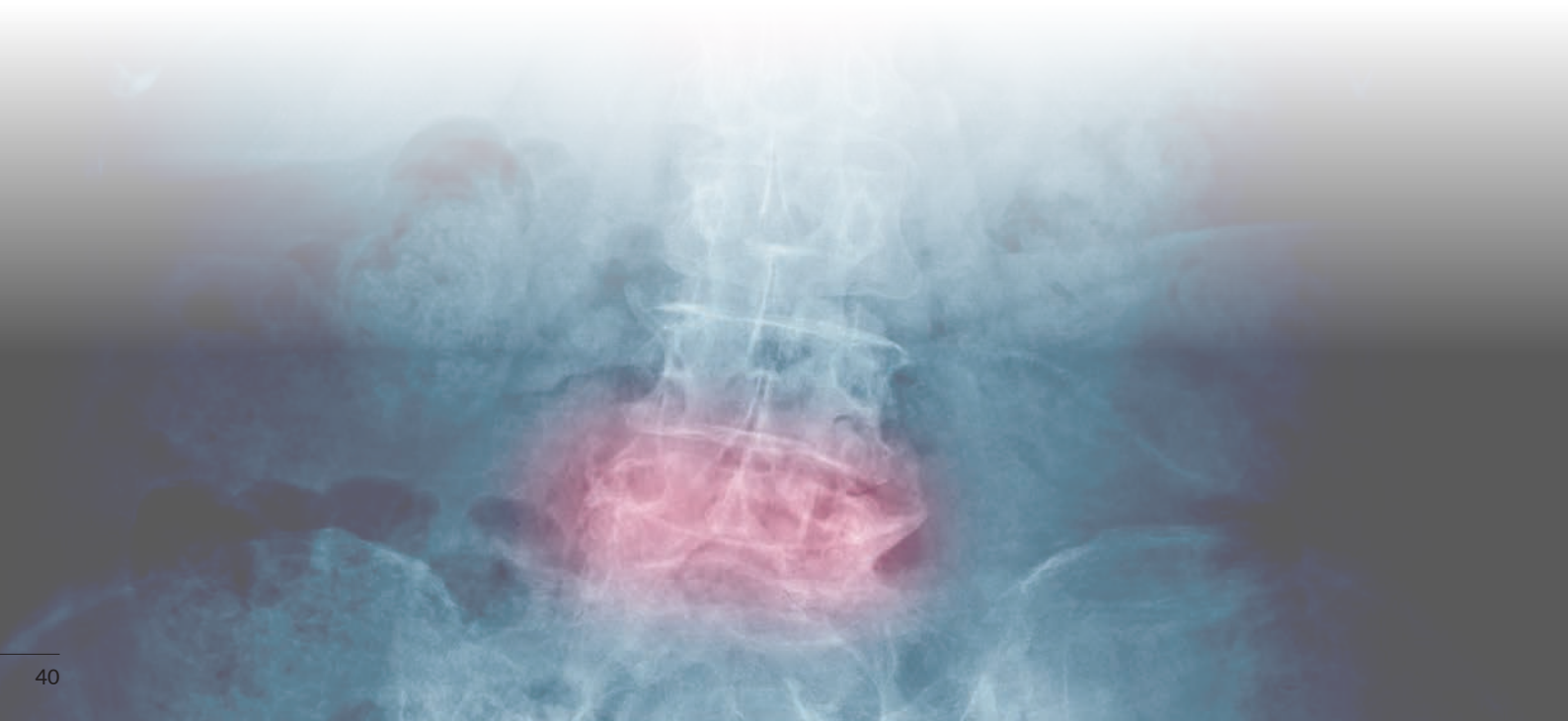
GO-ALIVE: Golimumab reduces AS signs and symptoms across 1 year, regardless of symptom duration

In the double-blind, placebo-controlled, phase III GO-ALIVE trial, 208 patients with AS were randomized 1:1 to receive intravenous golimumab 2 mg/kg at weeks 0 and 4, and then every 8 weeks, or placebo at weeks 0, 4 and 12, with crossover to golimumab at weeks 16 and 20, and every 8 weeks thereafter, through week 52.[1,2] The primary endpoint was an achievement of ≥20% improvement in SpondyloArthritis International Society (ASAS20) response criteria at week 16. The efficacy was evaluated through week 52, while the safety follow-up continued until week 60.

In the present post hoc analysis, patients were grouped into quartiles based on self-reported duration of inflammatory back pain (IBP) symptoms.[3] These include patients with early disease (n=60) (1st quartile defined as IBP <4 years) and those with late disease (n=52) (4th quartile defined as IBP >15.5 years).

Greater proportion of golimumab-treated patients achieved ASAS20

For the overall study population, baseline data indicated that patients with long-term symptoms of IBP (mean duration, 24 years) presented with more severe disease activity and were on average 10 years older than patients with recent-onset IBP (mean duration, 2–3 years).[3]



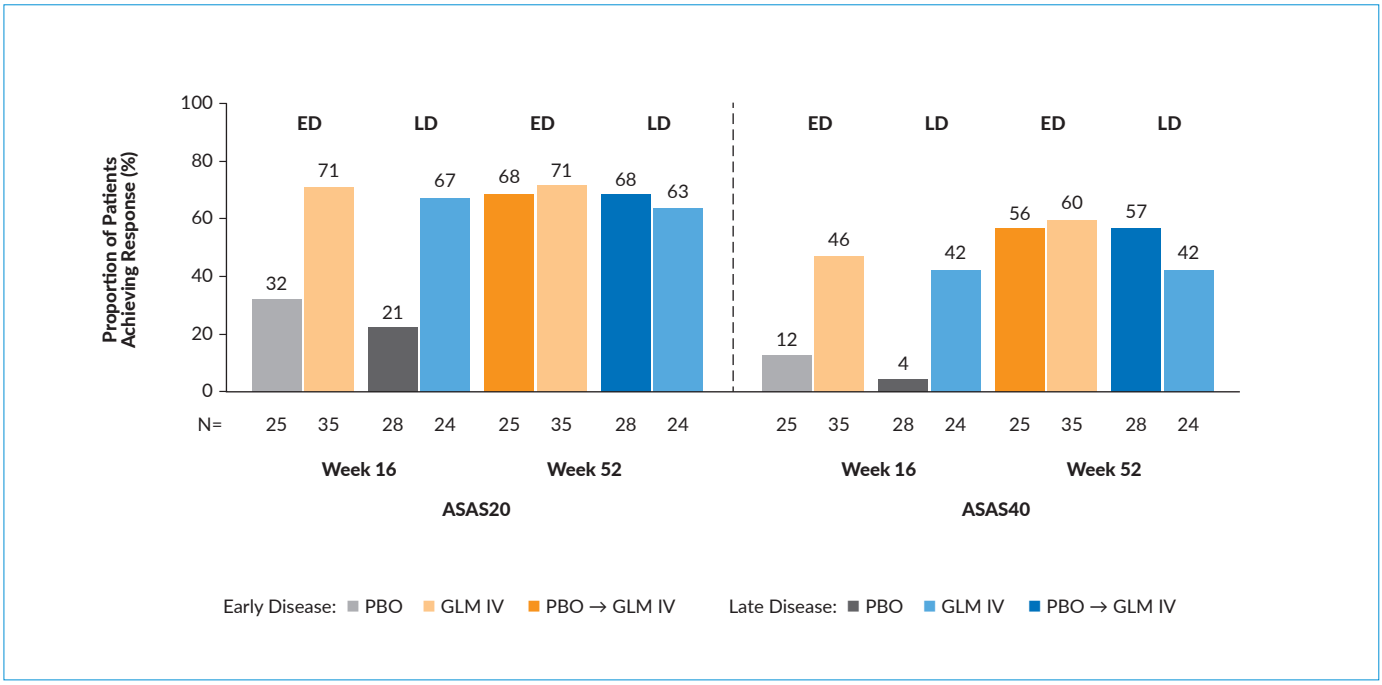


Figure 1. ASAS20/40 efficacy outcomes in patients with early versus late disease treated in GO-ALIVE. ASAS, SpondyloArthritis International Society; ED, early disease; GLM IV, intravenous golimumab; LD, late disease; PBO, placebo. Adapted from Deodhar et al. 2021.[3]

At week 16, a higher proportion of patients receiving golimumab versus placebo achieved primary and other important response criteria, regardless of the duration of IBP.[3] Among those with early disease, 71% of the golimumab-treated and 32% of the placebo-treated patients achieved ASAS20, while 67% and 21% of patients with late disease, respectively, achieved ASAS20 (**Figure 1**).[3] More patients in the golimumab group also achieved an ASAS40 response, 50% improvement of the initial Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50) and Ankylosing Spondylitis Disease Activity Score (ASDAS), as compared with the placebo group.

In both early and late disease subgroups, response rates were generally maintained through 1 year, including ASAS20 and ASAS40 (**Figure 1**).[3] Patients who crossed over to golimumab at week 16 demonstrated similar response rates at week 52, as compared with patients who received a full year of golimumab treatment, irrespective of symptom duration. Notably, more golimumab-treated patients with early versus late disease achieved BASDAI 50 and ASDAS inactive disease responses, which increased from week 16 to week 52.

The favorable benefit-risk profile of golimumab

No new safety signals were observed through week 60.[3] None of the patients experienced infusion reactions, serious infections, active tuberculosis, malignancies or death. During the placebo-controlled phase of the study (up to week 16), a higher proportion of patients with late versus early disease experienced treatment-emergent adverse events (golimumab: 46% and 29%; placebo: 39% and 12%).

CONCLUSIONS

- In the GO-ALIVE study, golimumab provided clinically meaningful improvements in signs and symptoms of ankylosing spondylitis across 1 year, regardless of the duration of inflammatory back pain symptoms.[3]
- More patients with early versus late disease achieved inactive disease with golimumab, underlining the importance of a prompt diagnosis and an early treatment initiation.

[1] Deodhar A et al. Safety and Efficacy of Golimumab Administered Intravenously in Adults with Ankylosing Spondylitis: Results through Week 28 of the GO-ALIVE Study. J Rheumatol. 2018; 45(3): 341–8.
[2] Reveille JD et al. Safety and Efficacy of Intravenous Golimumab in Adults with Ankylosing Spondylitis: Results through 1 Year of the GO-ALIVE Study. J Rheumatol. 2019; 46(10): 1277–83.
[3] Deodhar A et al. Efficacy and safety of intravenous golimumab in ankylosing spondylitis patients with early vs late disease through week 52 of GO-ALIVE study. EULAR 2021 Virtual Congress; 2–5 June 2021. Poster presentation POS0902.

Real-World Data on Biosimilars Versus Originator in **Juvenile Idiopathic Arthritis**

Comparative studies performed in adult patients with rheumatoid arthritis, ankylosing spondylitis or psoriasis led to the approval of two etanercept biosimilars for juvenile idiopathic arthritis (JIA)[1,2], but data on the use of these biosimilars in JIA patients in clinical practice is limited. At EULAR 2021, Prof. Gerd Horneff presented an analysis that assessed the efficacy and safety of etanercept biosimilars versus the originator in pediatric patients with JIA using data from the prospective BIKER registry.[3] In addition, the study evaluated the effect of switching from the originator to a biosimilar.

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Asklepios Kinderklinik
Sankt Augustin
Sankt Augustin, Germany

Etanercept biosimilars and the originator are equally effective in children with JIA

Between January 2017 and October 2020, a total of 439 patients with juvenile idiopathic arthritis (JIA) were treated with etanercept in 39 German centers; of these, 377 patients (85.9%) started therapy with the originator and 62 patients (14.1%) started with a biosimilar.[3] Of the 377 patients treated with the originator, 63 switched to a biosimilar and 3 of these patients re-switched to the originator. Biosimilars were prescribed in 17 centers (44%); in 12 centers (31%), etanercept biosimilars were used as first-line treatment.

The patients' characteristics and disease activity parameters at baseline were generally comparable between those primarily receiving a biosimilar and those receiving the originator.[3] However, biosimilar-treated patients were older at baseline than patients who received the originator (mean, 9.9 years vs 8.4 years) and more frequently had rheumatoid factor (RF)-negative polyarthritis (43.5% vs 34.7%), while patients treated with the originator more often received concomitant methotrexate (61.4% vs 50.0%).

Comparable reduction in disease activity between biosimilars and the originator

In terms of efficacy, the study found no significant differences between patients treated with a biosimilar or the originator.[3] As measured by Juvenile Arthritis Disease Activity Score (JADAS) 10, disease activity at baseline and the last follow-up was similar in the two treatment groups, suggesting that the use of all etanercept preparations led to a considerable reduction in disease activity (**Figure 1**).

Results further indicated that in patients switching from etanercept to a biosimilar, the improvement observed at the time of switching was sustained after switching and remained stable throughout treatment for all disease activity parameters, including JADAS minimal disease activity, JADAS remission and active joint count, as well as the physician and patient global visual analog scale (VAS).[3]

Similar safety profiles

A total of 66 adverse events (AEs) were reported in 45 patients upon biosimilar treatment, whereby 33 patients experienced 1 AE, while 12 patients reported up to 4 AEs.[3] Events of special interest (ESI) were hypersensitivity, injection site reaction, new onset of psoriasis, celiac disease, Crohn's disease, depression (each n=1), elevated transaminases (n=2) and disease deterioration (arthritis flare) (n=21).

In 20 patients, the biosimilar was discontinued.[3] In general, the incidence rate of AE and ESI was lower in etanercept-treated versus biosimilar-treated patients, but this result might be biased due to a lower patient number and shorter treatment time. The rate of local reactions at the injection site was 20% with biosimilars and 6.8% with the originator.

CONCLUSIONS

- This study showed no difference in the efficacy of etanercept biosimilars and the originator in children with juvenile idiopathic arthritis (JIA).[3]
- The safety profiles of biosimilars and the originator were comparable, with only injection site reactions occurring more frequently in patients treated with biosimilars.

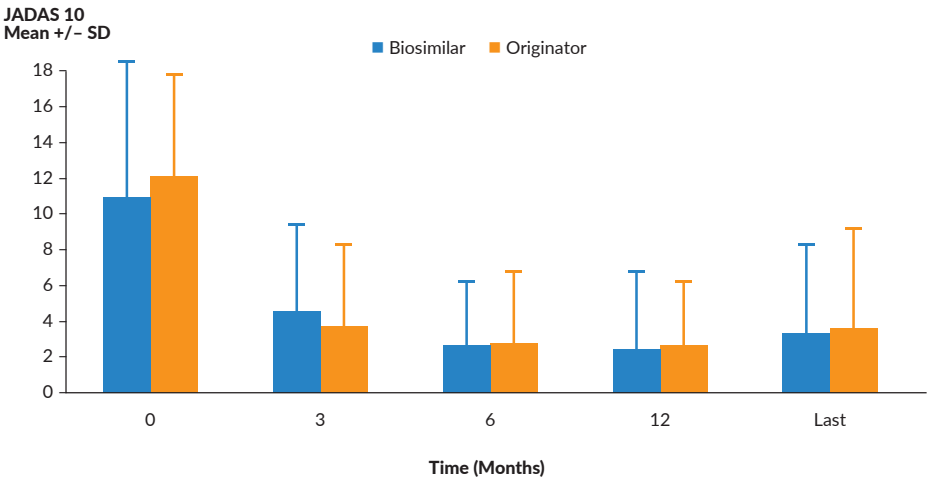

Figure 1. Improvement of the disease as assessed by JADAS10. JADAS, Juvenile Arthritis Disease Activity Score; SD, standard deviation. Adapted from Horneff et al. 2021.[3]

[1] BENEPALI® (etanercept). Information for healthcare professionals. Compendium. [Accessed September 2021]. Available from: https://compendium.ch/product/1395972-benepali-inj-los-50-mg-ml-fertigpen/mpro.
[2] Erelzi® (etanercept). Information for healthcare professionals. Compendium. [Accessed September 2021]. Available from: https://compendium.ch/product/1372342-erelzi-inj-los-50-mg-ml/mpro.
[3] Horneff G et al. Comparative analysis of etanercept biosimilar and originator use in clinical practice: data from the German BIKER- Registry. EULAR 2021 Virtual Congress; 2–5 June 2021. Oral presentation OP0163.

XELJANZ® bei RA[Δ,§]:

- Bis zu **9,5 Jahre** Beobachtungszeitraum[#,3]
- **>22'000** Patientenjahre unter XELJANZ®-Therapie in klinischen Studien[4]
- **>115'000** Patienten Real-World-Erfahrung[#,3]

Δ Rheumatoide Arthritis (RA): Mono- oder Kombinationstherapie mit einem nicht biologischen DMARD bei erwachsenen Patienten mit mittelschwerer bis schwerer aktiver RA, bei denen eine vorherige Therapie mit Methotrexat nicht angesprochen hatte oder nicht vertragen wurde.[1]

§ 5 mg zweimal täglich ist die einzige zugelassene Tofacitinib-Dosierung für die Behandlung von rheumatoider Arthritis.[1]

Therapieabbruchrate in dieser Langzeit-Erhaltungsstudie insgesamt 52% (24% aufgrund von Nebenwirkungen und 4% aufgrund von mangelnder Wirksamkeit). Tofacitinib-Gesamtexposition war 16 291 Patientenjahre. Ab Monat 72 sind die Daten mit Vorsicht zu interpretieren aufgrund kleiner Patientenzahlen.[3]

* Angaben zur Spezialitätenliste und Limitatio finden Sie unter http://www.spezialitätenliste.ch/ShowPreparations.aspx

XELJANZ®
(tofacitinib citrate)

DMARD: disease-modifying antirheumatic drug; **JAK:** Januskinase; **RA:** rheumatoide Arthritis.

Gekürzte Fachinformation – XELJANZ® (Tofacitinib)
Indikationen: Rheumatoide Arthritis (RA): Mono- oder Kombinationstherapie mit einem nicht biologischen DMARD bei erwachsenen Patienten mit mittelschwerer bis schwerer aktiver RA, bei denen eine vorherige Therapie mit Methotrexat nicht angesprochen hatte oder nicht vertragen wurde. Psoriasis-Arthritis (PsA): Erwachsene Patienten mit aktiver PsA in Kombination mit einem konventionellen, synthetischen DMARD zur Besserung von Symptomen und der körperlichen Funktionsfähigkeit, bei Patienten die auf eine vorherige Therapie mit einem DMARD unzureichend angesprochen oder diese nicht vertragen hatten. Colitis ulcerosa (CU): Erwachsene Patienten mit mittelschwerer bis schwerer aktiver CU, die auf eine vorherige Therapie mit Kortikosteroiden, Azathioprin, 6-MP oder einen TNF-Antagonisten unzureichend angesprochen haben, nicht mehr darauf ansprechen oder diese Therapien nicht vertragen haben. **Dosierung:** RA: 2× täglich 5 mg. In Kombination mit starken Inhibitoren von CYP3A4 oder CYP2C19, nicht mehr als 5 mg 1× täglich. PsA: 5 mg 2× täglich in Kombination mit einem csDMARD. In Kombination mit starken Inhibitoren von CYP3A4 oder CYP2C19, nicht mehr als 5 mg 1× täglich. CU: Induktion: 10 mg 2× täglich für min. 8 Wochen bis max. 16 Wochen; Erhaltung: 5 mg 2× täglich; In Kombination mit starken Inhibitoren von CYP3A4 oder CYP2C19: nicht mehr als 5 mg 2× täglich (falls sonst 10 mg 2× täglich) bzw. 5 mg 1× täglich (falls sonst 5 mg 2× täglich). **Kontraindikationen:** Aktive, schwere Infektionen, schwere Leberinsuffizienz und Überempfindlichkeit gegen einen Inhaltsstoff. **Vorsichtsmassnahmen:** XELJANZ® darf nicht an Patienten mit aktiver systemischer oder lokalisierter Infektion verabreicht werden. Erhöhtes Risiko für kardiovaskuläre Ereignisse, maligne Erkrankungen, venöse Thromboembolien und Gesamtmortalität. XELJANZ® sollte bei Patienten über 65 Jahren, bei Patienten, die gegenwärtig rauchen oder früher geraucht haben oder bei Patienten mit anderen Risikofaktoren für kardiovaskuläre bzw. maligne Erkrankungen nur dann eingesetzt werden, wenn keine geeigneten Behandlungsalternativen zur Verfügung stehen. Patienten regelmässig vor und während der Behandlung auf venöse Thromboembolie-Risikofaktoren hin beurteilen. Vorsicht bei Patienten mit Tuberkulose, chronischen oder rekurrierenden Infektionen, chronischen Lungenerkrankungen, Virus- und Tumorerkrankungen (inklusive lymphoproliferative Erkrankungen und nicht-melanozytärer Hautkrebs), erhöhtem Risiko einer Magen-Darm-Perforation, und bei älteren Patienten sowie Diabetikern und Patienten mit multiplen Allergien in der Vorgeschichte. Ein erhöhtes Risiko von Herpes zoster wurde beobachtet. Regelmässige Hautuntersuchung bei Patienten mit erhöhtem Hautkrebsrisiko empfohlen (Risiko ggf. unter 2× täglich 10 mg erhöht). Dosisanpassungen aufgrund Beeinträchtigung der Leber- und Nierenfunktion sind gegebenenfalls erforderlich. Vor und während der Behandlung sind Blutbildkontrollen empfohlen (Prüfung auf Lymphopenie, Neutropenie und Anämie sowie Untersuchung der Blutfettwerte), gegebenenfalls sind Dosisanpassungen erforderlich. Patienten mit RA oder PsA weisen ein erhöhtes Risiko für kardiovaskuläre Erkrankungen auf und sollten auf Risikofaktoren hin überwacht werden. Vor der Behandlung Impfstatus aktualisieren; Lebendimpfstoffe dürfen nicht direkt vor und während der Therapie mit XELJANZ® angewendet werden. Kombination mit Biologika und starken Immunsuppressiva ist zu vermeiden. Gewisse Risiken sind unter 10 mg 2× täglich höher als unter 5 mg 2× täglich. **Interaktionen:** Vorsicht bei gleichzeitiger Anwendung von potenten CYP3A4 Inhibitoren, potenten CYP3A4 Induktoren, mittelstarken CYP3A4 Inhibitoren welche gleichzeitig starke CYP2C19 Inhibitoren sind, und OCT Substraten. **Unerwünschte Wirkungen:** Schwerwiegende Infektionen, Nasopharyngitis, Harnwegsinfektion, Bronchitis, Herpes zoster, Grippe, Sinusitis, Pharyngitis, Pneumonie, Virusinfektion, Sepsis, solider Tumor, nicht-melanozytärer Hautkrebs (NMSC), Lungenkrebs, Lymphom, Anämie, Leukopenie, Neutropenie, Lymphopenie, Hyperlipidämie, Cholesterin im Blut erhöht, Kopfschmerz, Parästhesie, Myokardinfarkt, Hypertonie, venöse Thromboembolien, inkl. Lungenembolien und tiefe Venenthrombosen, Husten, Dyspnoe, Diarrhö, Übelkeit, Dyspepsie, Abdominalschmerz, Erbrechen, Gastritis, Gamma-Glutamyltransferase erhöht, Ausschlag, Arthralgie, Kreatinphosphokinase im Blut erhöht, Ödem peripher, Fieber, Ermüdung u. a. **Packungen:** 5 mg und 10 mg: 56 Filmtabletten. Verkaufskategorie B. **Zulassungsinhaberin:** Pfizer AG, Schärenmoosstrasse 99, 8052 Zürich. Ausführliche Informationen siehe Arzneimittel-Fachinformation unter www.swissmedicinfo.ch. (V049)

Die abgebildete Tablette kann von der Originalgrösse abweichen.

Pfizer AG
Schärenmoosstrasse 99
Postfach
8052 Zürich

Referenzen: 1. Fachinformation XELJANZ®, www.swissmedicinfo.ch. **2.** BAG Spezialitätenliste. www.spezialitätenliste.ch; Stand Januar 2021. **3.** Wollenhaupt J, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019; 21(1): 89. **4.** Cohen SB, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. RMD Open. 2020;6:e001395.

Referenzen sind auf Anfrage erhältlich.

PP-XEL-CHE-1206 Aug 2021

Benlysta is
Designed for

Lupus

Superior disease activity reduction compared to standard therapy alone[1]

Reduction of disease activity in patients aged 5 years and older (infusion solution) and in patients aged 18 years and older (subcutaneous injection) respectively with active autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab has not been studied in patients with severe active central nervous system lupus or severe active lupus nephritis.[1]

BENLYSTA powder for making an infusion solution, solution for subcutaneous injection. **AI:** Belimumab. **I:** Reduction of disease activity in patients aged 5 years and older (infusion solution) and in patients aged 18 years and older (subcutaneous injection) respectively with active autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab has not been studied in patients with severe active central nervous system lupus or severe active lupus nephritis. **D:** Patients ≥ 5 years: *Infusion solution:* 10 mg/kg on Days 0, 14, 28, and at 4-weeks intervals thereafter. I.v.-infusion over a 1 h period; must not be administered as an i.v. push or bolus. Premedication with an oral antihistamine, with or without an antipyretic, may be administered. Patients should be monitored during and for an appropriate period of time after administration. Patients ≥ 18 years: *Solution for subcutaneous injection:* 200 mg once a week, on the same day of the week (independent of body weight). S.c.-injection (abdomen or thigh). Suitable training of patient in the technique associated with s.c. injection and the perception of signs and symptoms of hypersensitivity reactions. Switch from i.v.- to s.c.-treatment: first s.c. dose approx. 2 weeks after the last i.v. dose. *General:* consider discontinuing treatment if there is no improvement in the control of the disease after 6 months. For elderly patients and patients with renal impairment, dosage adjustment is not recommended. Hepatic impairment: see product information. **CI:** Hypersensitivity to one of the ingredients. **W/P:** Infusion-, injection- and hypersensitivity reactions are possible, which can be severe, or fatal (delay in onset, and recurrence after initial resolution possible). Patients should be made aware of potential risks and signs of such reactions. Increased risk of infection possible. Presenting neurological symptoms, possibility of progressive multifocal leukoencephalopathy (PML) should be considered. Increased potential risk for development of malignancies. Before treatment with belimumab, the patient's risk for depression or suicide must be carefully evaluated and the patient must be monitored accordingly during treatment. The physician must be contacted in the event of new or worsening psychiatric symptoms. Application in combination with other B-cell-targeted therapy or cyclophosphamide i.v. was not studied. Live vaccines should not be given for 30 days before or concurrently with Belimumab. **IA:** No drug interaction studies have been conducted. Evidence of increased clearance of belimumab i.v. when co-administrated with steroids and ACE inhibitors. **P/L:** *Pregnancy:* Belimumab should only be used if the potential benefit to the mother justifies the potential risk to the foetus. If indicated, women of childbearing age should use adequate contraceptive measures while being treated and for at least four months after the last treatment. *Lactation:* Safety not verified. In consideration of all aspects it is recommended to consider discontinuing breast-feeding. **UE:** *Very common:* Infections, nausea, diarrhoea. *Common:* Hypersensitivity-, infusion- and injection-related reaction, pyrexia, (rhino)pharyngitis, bronchitis, cystitis, gastroenteritis viral, pain in extremity, insomnia, depression, migraine, leukopenia; reactions at the administration site (s.c.-injection). *Uncommon:* a. o. bradycardia, anaphylactic reaction, angioedema, Suicidal thoughts, suicidal behavior, rash. **Store:** at + 2 °C to + 8 °C, do not freeze. **P:** Powder for making an infusion solution: 120 mg and 400 mg vial. Solution for subcutaneous injection: Autoinjector 200 mg (1 ml) ×1 and ×4. **DC:** Vial: A. Autoinjector: B. **Last updated:** February 2020 (infusion solution), October 2019 (subcutaneous injection). GlaxoSmithKline AG, 3053 Münchenbuchsee. Detailed information you can find under www.swissmedicinfo.ch. Please report adverse drug reactions under pv.swiss@gsk.com.

Reference: 1. Fachinformation Benlysta, www.swissmedicinfo.ch.

GlaxoSmithKline AG, Talstrasse 3–5, CH-3053 Münchenbuchsee,
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PM-CH-BEL-ADVT-190002-5/2020

Benlysta (belimumab)