Drug Class Review
Targeted Immune Modulators

Preliminary Scan Report #1
July 2017

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #5: June 2016 (searched through January 2016)

Date of Last Preliminary Update Scan Report

None since most recent update report.

Scope and Key Questions

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. The RTI-UNC Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and we based the eligibility criteria for studies on these preliminary questions. Representatives of organizations participating in the Drug Effectiveness Review Project, in conjunction with experts in the fields of health policy, rheumatology, pharmacotherapy, and research methods reviewed, revised and approved the questions and outcome measures. The participating organizations approved the following key questions:

1. How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and plaque psoriasis?
2. What are the comparative incidence and severity of harms associated with the use of these drugs?
3. Do the included drugs differ in effectiveness or harms in the following subgroups:
   a. Different genders or different racial, age, or socioeconomic groups?
   b. Patients with comorbidities?
   c. Patients taking other commonly prescribed drugs?
   d. Patients with early aggressive compared with persistent rheumatoid arthritis?
Inclusion Criteria

Populations

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Crohn’s disease
- Ulcerative colitis
- Plaque psoriasis

Interventions

Table 1. Included interventions

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Mechanism of action</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Apremilast</td>
<td>Otezla®</td>
<td>PDE4 inhibitor</td>
<td>Adult moderate to severe plaque psoriasis and psoriatic arthritis</td>
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<tr>
<td>Abatacept</td>
<td>Orencia®</td>
<td>CD80/86–CD28 T-cell co-stimulation modulator</td>
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<td>Humira®</td>
<td>TNF Inhibitor</td>
<td>Rheumatoid arthritis</td>
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<td>Psoriatic arthritis, ankylosing spondylitis</td>
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<td>Juvenile idiopathic arthritis (4 years of age and older)</td>
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<td>Adult Crohn’s disease</td>
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<td>Ulcerative colitis</td>
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<td>Alefacept</td>
<td>Amevive®</td>
<td>CD2 antagonist</td>
<td>Plaque psoriasis</td>
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<td>Anakinra</td>
<td>Kineret®</td>
<td>IL-1 Inhibitor</td>
<td>Rheumatoid arthritis</td>
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<td>Neonatal-Onset Multisystem Inflammatory Disease (NOMID)</td>
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<td>Canakinumab</td>
<td>Ilaris®</td>
<td>IL-1β Inhibitor</td>
<td>Systemic Juvenile Idiopathic Arthritis (2 years and older)</td>
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<td>Certolizumab pegol</td>
<td>Cimzia®</td>
<td>TNF Inhibitor</td>
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<td>Crohn’s disease</td>
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<td>Etanercept</td>
<td>Enbrel®</td>
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<td>Infliximab</td>
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<td>Xeljanz®</td>
<td>JAK inhibitor</td>
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<td>Stelara®</td>
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<td>Vedolizumab</td>
<td>Entyvio®</td>
<td>α4β7 integrin inhibitor</td>
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<td>Adult Crohn's disease</td>
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**Efficacy/effectiveness outcomes**

- Health outcomes:
  - Quality of Life
  - Functional capacity
  - Employability, productivity
  - Clinical improvement
  - Disease remission
  - Pain
  - Reduction in the number of swollen or tender joints
  - Reduction in disease-related hospitalizations
  - Reduction in disease-specific mortality
  - Rebound / flare
  - Joint destruction
  - Steroid withdrawal

- If no studies with health outcomes were available, we included intermediate outcomes:
  - Radiological outcomes

**Harms/tolerability outcomes**

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events, including:
  - Lymphoma
  - All malignancies
  - Serious infectious diseases
  - Herpes zoster
  - Opportunistic infections

- Mortality
Study eligibility criteria
For efficacy/effectiveness:

- Outpatient study population
- Head-to-head randomized controlled clinical trials comparing one TIM drug to another
  - ≥12 weeks study duration

For harms/tolerability:

- Outpatient study population
- Head-to-head randomized controlled clinical trials comparing one TIM drug to another
  - ≥12 weeks study duration
- Head-to-head observational studies were reviewed for harms
  - ≥12 weeks study duration
- N≥1000

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from December 2015 to June 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrdrresearch.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - “Our Publications” and “Our Databases”). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.
RESULTS

New Drugs

**Identified in this Preliminary Update Scan**

**Newly Approved Drugs**

Sarilumab (Kevzara®): interleukin-6 receptor antagonist approved on 5/22/17 for the treatment of adults with moderate to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). Administered by subcutaneous injection. May be used as a monotherapy or in combination with methotrexate or other conventional DMARDs.

Brodalumab (Siliq™): human interleukin-17A receptor antagonist approved on 2/15/17 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. Administered by subcutaneous injection.

Ixekizumab (Taltz™): humanized interleukin-17A antagonist approved on 3/22/16 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Administered by subcutaneous injection.

**Newly Approved Biolosimilar Products**

Infliximab (Renflexis™): injectable TNF blocker approved on 4/21/2017 for Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Merck plans to market in 6 months, assuming no court delays.

Adalimumab (Amjevita™): injectable approved on 9/23/2016 for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis, and plaque psoriasis. May be delayed due to court action by Amgen.


*We identified 2 drugs that are currently in the pipeline:*
- **Sirukumab** is a humanized anti-interleukin-6 monoclonal antibody under development for the treatment of rheumatoid arthritis. Currently in phase III trials with a BLA submitted to the FDA on 9/23/2016.
- **Risankizumab** is an anti-IL-23 antibody being developed for the treatment of psoriasis, Crohn’s disease and psoriatic arthritis. Currently in phase III trials. Anticipated launch date is 2019.

**Identified in previous Preliminary Update Scans**

No scan since most recent update report.
New Serious Harms (e.g., Boxed Warnings)

**Identified in this Preliminary Update Scan**
No new serious harms were identified in this scan.

**Identified in previous Preliminary Update Scans**
No scan since most recent update report.

Comparative Effectiveness Reviews

**Identified in this Preliminary Update Scan**
We identified 1 potentially relevant health technology assessment that could be used to answer specific pieces of an update report. This review pertains to the use of TNF-a inhibitors for ankylosing spondylitis.


We also identified an Agency for Healthcare Research & Quality comparative effectiveness review that is currently in progress pertaining to drug therapy, including targeted immune modulators, for the treatment of rheumatoid arthritis in adults. The review protocol was published in May 2017. [https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2475](https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2475). The completion date for this review is unknown at this time.

**Identified in previous Preliminary Update Scans**
No other scans since most recent update report.

Randomized Controlled Trials

**Trials identified since the most recent Full Report**
Medline searches for this scan resulted in 199 citations. Of those, 12 were considered potentially relevant and includable in this scan. Four trials evaluated head-to-head drug comparisons, while 3 trials evaluated head-to-head device or delivery methods comparisons. Four trials evaluated biosimilars to their reference drugs, and 1 trial compared a drug in development (risankizumab) to an approved drug (ustekinumab).

Study characteristics are listed in Table 2 below. Abstracts of these trials are available in Appendix A.

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TIMs
Table 2. New head-to-head trials (N=7)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Population</th>
<th>Comparison</th>
<th>Focus</th>
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<td><strong>Head-to-head drug</strong></td>
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<td>Blauvelt, 2017 CLEAR</td>
<td>676</td>
<td>52 weeks</td>
<td>Moderate-to-severe plaque psoriasis*</td>
<td>Secukinumab vs. ustekinumab</td>
<td>Clinical improvement (skin clearing), quality of life, pain, functional capacity (activity impairment)</td>
</tr>
<tr>
<td>Dennehy, 2016 UNCOVER-3</td>
<td>NR</td>
<td>60 weeks</td>
<td>Moderate-to-severe plaque psoriasis</td>
<td>Ixekizumab vs. etanercept</td>
<td>Disease activity (nail psoriasis)</td>
</tr>
<tr>
<td>Porter, 2016 ORBIT NCT01021735</td>
<td>295</td>
<td>52 weeks</td>
<td>Rheumatoid arthritis</td>
<td>Rituximab vs. adalimumab or etanercept</td>
<td>Disease activity, adverse events</td>
</tr>
<tr>
<td>Valenzuela, 2016</td>
<td>1,092</td>
<td>12 weeks</td>
<td>Moderate-to-severe plaque psoriasis</td>
<td>Tofacitinib vs. etanercept</td>
<td>Quality of life, patient-reported outcomes</td>
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<tr>
<td><strong>Head-to-head delivery method</strong></td>
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<tr>
<td>Burmester, 2016 SUMMACTA NCT01194414</td>
<td>1,262</td>
<td>97 weeks (rerandomized after 24 weeks)</td>
<td>Rheumatoid arthritis with inadequate response to DMARDs</td>
<td>SC ticilizumab vs. IV tocilizumab</td>
<td>Disease activity, remission, disability, adverse events</td>
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<tr>
<td>Callis, 2017 UNCOVER-A NCT01777191</td>
<td>204</td>
<td>24 weeks</td>
<td>Moderate-to-severe plaque psoriasis</td>
<td>Ixekizumab via PFS vs. Ixekizumab via autoinjector</td>
<td>Efficacy (PASI), adverse events.</td>
</tr>
<tr>
<td>Tlustochowicz, 2016</td>
<td>221</td>
<td>52 weeks</td>
<td>Active rheumatoid arthritis</td>
<td>Secukinumab IV vs. secukinumab SC</td>
<td>Disease activity, pain, adverse events</td>
</tr>
</tbody>
</table>

*New FDA Approved Indication for secukinumab, January 2016

Trials of Biosimilar Drugs (N=4)

- Biosimilar adalimumab (Amjevita): 1 (vs. reference adalimumab in rheumatoid arthritis)
- Biosimilar infliximab (Inflectra): 3 (vs. reference infliximab in ankylosing spondylitis [1] or rheumatoid arthritis [2])

Trials of Drugs in Development (N=1)

- Risankizumab: 1 (vs. ustekinumab in moderate-to-severe plaque psoriasis)

**SUMMARY**

Since the last update report, we have identified 3 newly approved drugs, 3 newly approved biosimilar products, and 2 drugs currently in development (Phase III). We identified 1 comparative effectiveness review of ankylosing spondylitis that could be used to answer specific pieces of an update report on this topic, and an ongoing review by the Agency for Healthcare Research and Quality on rheumatoid arthritis treatment. In terms of new evidence, we have identified 12 potentially relevant trials; 4 head-to-head comparisons of drugs (1 of a new drug, 1 of a previously included drug in a newly approved population/indication, 2 = new comparisons of drugs already in report), 3 trials device or delivery method comparisons (1 of a new drug, 1 = new indication for a drug already in report), 4 trials of a biosimilar versus the reference drug, and 1 trial of a drug in development, not due to be launched until 2019.
APPENDIX A. HEAD-TO-HEAD TRIALS OF TARGETED IMMUNE MODULATORS


BACKGROUND: Secukinumab demonstrated superior efficacy to ustekinumab at week 4 and week 16 of the CLEAR study, with comparable safety, in subjects with moderate-to-severe plaque psoriasis.

OBJECTIVE: To compare the efficacy and safety of secukinumab and ustekinumab use over 52 weeks.

METHODS: Analysis of 52-week data from CLEAR, a randomized, double-blind, phase 3b study.

RESULTS: Among 676 randomized subjects, secukinumab demonstrated superiority to ustekinumab at week 52 in the proportion of subjects with >=90% improvement in Psoriasis Area and Severity Index (PASI 90) (76% vs 61% [P < .0001]); PASI 100 responses were 46% versus 36% (P = .0103) and Investigator's Global Assessment responses of clear/almost clear skin were 80% versus 65% (P < .0001). Subjects on secukinumab reported greater reductions in psoriasis-related pain, itching, and scaling, and greater improvement across all quality-of-life measures evaluated (Dermatology Life Quality Index [DLQI], EuroQoL 5-Dimension Health Questionnaire, Work Productivity and Activity Impairment Questionnaire-Psoriasis, and Health Assessment Questionnaire-Disability Index). At week 52, 72% of subjects on secukinumab versus 59% on ustekinumab (P = .0008) reported no impact of skin disease on their lives (DLQI 0/1 response). Safety and tolerability was comparable.

LIMITATIONS: There was no placebo arm.

CONCLUSION: In this head-to-head, double-blind study, secukinumab demonstrated sustained superior efficacy in comparison with ustekinumab in clearing skin through week 52, greater improvement in quality of life, and a favorable and comparable safety profile.

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OBJECTIVES: To evaluate the long-term efficacy and safety of subcutaneous (SC) tocilizumab (TCZ) versus intravenous (IV) TCZ, including switching formulations, in patients with rheumatoid arthritis (RA) and inadequate response to disease-modifying antirheumatic drugs (DMARDs).

METHODS: Patients (n=1262) were randomised 1:1 to receive TCZ-SC 162 mg weekly (qw)+placebo-IV every four weeks (q4w) or TCZ-IV 8 mg/kg q4w+placebo-SC qw in combination with DMARD(s). After a 24-week double-blind period, patients receiving TCZ-SC were re-randomised 11:1 to TCZ-SC (n=521) or TCZ-IV (TCZ-SC-IV, n=48), and patients receiving TCZ-IV were re-randomised 2:1 to TCZ-IV (n=372) or TCZ-SC (TCZ-IV-SC; n=186). Maintenance of clinical responses and safety through week 97 were assessed.
RESULTS: The proportions of patients who achieved American College of Rheumatology (ACR)20/50/70 responses, Disease Activity Score in 28 joints remission and improvement from baseline in Health Assessment Questionnaire Disability Index >=0.3 were sustained through week 97 and comparable across arms. TCZ-SC had a comparable safety profile to TCZ-IV through week 97, except that injection site reactions (ISRs) were more common with TCZ-SC. Safety profiles in patients who switched were similar to those in patients who received continuous TCZ-SC or TCZ-IV treatment. The proportion of patients who developed anti-TCZ antibodies remained low across treatment arms. No association between anti-TCZ antibody development and clinical response or adverse events was observed.

CONCLUSIONS: The long-term efficacy and safety of TCZ-SC was maintained and comparable to that of TCZ-IV, except for ISRs. Profiles in patients who switched formulations were comparable to those in patients who received TCZ-IV or TCZ-SC. TCZ-SC provides additional treatment options for patients with RA.

Trial registration number: nct01194414.


BACKGROUND: The efficacy of ixekizumab, an anti-interleukin-17A (anti-IL-17A) monoclonal IgG4 antibody, was demonstrated in moderate-to-severe psoriasis patients when administered via prefilled syringe (PFS).

OBJECTIVE: To evaluate the effect of two drug delivery devices on the pharmacokinetics (PK) of ixekizumab as well as efficacy and safety with both devices.

METHODS: In the first 12 weeks of an open-label, phase 3 study, moderate-to-severe psoriasis patients were randomized to ixekizumab delivery via PFS or autoinjector device. Randomization was stratified by weight (<80 kg, 80-100 kg, >100 kg), injection assistance (yes/no) and injection site (arm, thigh or abdomen). Following a 160-mg initial dose at week 0, patients received subcutaneous 80-mg ixekizumab as a single injection every 2 weeks for 12 weeks. Blood samples were collected following the initial 160-mg dose on days 2, 4, 7, 10 and 14 for PK analysis. Primary PK parameters were maximum concentration (C<sub>max</sub>) and area under the curve (AUC<sub>0-tlast</sub>) where t<sub>last</sub> is the time of last sample (14 days +/- 24 h). Efficacy was assessed by percent improvement on the Psoriasis Area and Severity Index (PASI) at week 12. Adverse event reporting, vital signs and clinical laboratory data were used to evaluate safety.

RESULTS: Of 204 randomized patients, 192 were included in the PK analysis (PFS: 94; autoinjector: 98). The PFS and autoinjector showed similar geometric mean C<sub>max</sub> (90% CI [15.0 mug/mL (13.9-16.1)] vs. 14.8 mug/mL (13.8-15.9]) and geometric mean AUC<sub>0-tlast</sub> (90% CI [157 mug x day/mL (147-168] vs. 154 mug x day/mL (144-165]). When comparing C<sub>max</sub> and AUC<sub>0-tlast</sub> of the autoinjector to PFS, the geometric LS mean ratios were...
0.97. At week 12, mean percent PASI improvement (via modified baseline observation carried forward) was similar with the PFS (89.3%) and autoinjector (86.9%). Both devices had safety results that were consistent with the known safety profile of ixekizumab.

CONCLUSION: The PK, efficacy and safety of ixekizumab administered subcutaneously by PFS and autoinjector were similar. Clinicaltrials.gov number: NCT01777191 https://clinicaltrials.gov/ct2/show/NCT01777191.

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BACKGROUND: Ixekizumab, a monoclonal antibody that selectively targets interleukin-17A, has been established as safe and effective in 3 Phase 3 trials for the treatment of moderate to severe plaque psoriasis. The lifetime incidence of psoriatic nail disease is 80%-90% of patients, and approximately 50% of patients with psoriasis have nail involvement.

MATERIALS AND METHODS: The design of UNCOVER-3, a Phase 3, multicenter, double-blind, placebo- and active-controlled trial that evaluated the efficacy and safety of ixekizumab for moderate to severe psoriasis, has been published previously. Patients were randomized to receive blinded placebo, etanercept (50 mg twice weekly) or 80 mg ixekizumab every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W) for 12 weeks. At week 12, all patients were assigned to open-label ixekizumab 80 mg every 4 weeks through week 60. In this 60-week post hoc subset analysis, we evaluated only those patients with significant baseline nail involvement, defined as fingernail NAPSI ≥16 and at least 4 fingernails involved.

RESULTS: Ixekizumab Q2W or Q4W resulted in greater improvement in nail psoriasis than placebo or etanercept by week 12 of administration, as measured by percent NAPSI reduction (IXEQ2W 39% improvement, IXEQ4W 40%, etanercept 28%, placebo -4.7%). At week 24, significantly more patients receiving ixekizumab exhibited no signs of nail involvement (IXEQ2W/Q4W 34%, IXEQ4W/Q4W 30%). Similar gains were observed at 60 weeks in all treatment groups.

CONCLUSION: Ixekizumab led to improvement in fingernail psoriasis by week 12 compared with placebo. Continued improvement in fingernail psoriasis with ixekizumab was observed, with >50% of patients achieving complete fingernail psoriasis resolution (NAPSI=0) at week 60.


AIM: In this study, efficacy, tolerability and safety of biosimilar adalimumab (Exemptia; Zydus Cadila) was compared with reference adalimumab (Humira; AbbVie) in patients with moderate to severe rheumatoid arthritis (RA).
METHOD: In this multicentre, prospective, randomized, double-blind, active controlled parallel arm study, 120 patients with moderate to severe RA were given 40 mg of either test adalimumab (Exemptia) or reference adalimumab (Humira) by subcutaneous route every other week for 12 weeks. The primary endpoint was proportion of responders in two treatment groups by American College of Rheumatology 20 (ACR20) at week 12. The secondary endpoints were change in Disease Activity Score of 28 joints - C-reactive protein (DAS28-CRP) and proportion of patients with an ACR50 and ACR70 response in two treatment groups at week 12. Safety outcomes were also assessed.

RESULTS: After 12 weeks, patients treated every other week with test adalimumab (Zydus Cadila) had statistically similar response rates as compared to reference adalimumab (AbbVie): ACR20 (82% vs. 79.2%; P > 0.7); ACR50 (46%, vs. 43.4%; P > 0.7); ACR70 (14% vs. 15.1%; P > 0.8). The change in DAS28-CRP score was -2.1 +/- 1.09 and -2.1 +/- 1.21, in test and reference products, respectively. It was statistically significant compared to baseline, but not significantly different between the two products. Three serious adverse events and no death was reported during the study. Both adalimumab preparations were safe and well tolerated in this study.

CONCLUSION: The results demonstrated biosimilarity with respect to efficacy, tolerability and safety of test adalimumab (Exemptia) and reference adalimumab (Humira) in patients with moderate to severe RA.

BACKGROUND: Interleukin-23 is thought to be critical to the pathogenesis of psoriasis. We compared risankizumab (BI 655066), a humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit and thus prevents interleukin-23 signaling, and ustekinumab, an interleukin-12 and interleukin-23 inhibitor, in patients with moderate-to-severe plaque psoriasis.

METHODS: We randomly assigned a total of 166 patients to receive subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16). The primary end point was a 90% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12.

RESULTS: At week 12, the percentage of patients with a 90% or greater reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab (P<0.001); the percentage of patients with a 100% reduction in the PASI score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 or 180 mg of risankizumab. In the 18-mg and 90-mg risankizumab groups and the ustekinumab group, 5 patients (12%), 6 patients (15%), and 3 patients (8%), respectively, had serious adverse events, including two basal-cell carcinomas and one major cardiovascular adverse event; there were no serious adverse events in the 180-mg risankizumab group.

CONCLUSIONS: In this phase 2 trial, selective blockade of interleukin-23 with risankizumab was associated with clinical responses superior to those associated with ustekinumab.
This trial was not large enough or of long enough duration to draw conclusions about safety. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT02054481).


**BACKGROUND:** CT-P13 (Remsima, Inflectra) is a biosimilar of the infliximab reference product (RP; Remicade) and is approved in Europe and elsewhere, mostly for the same indications as RP. The aim of this study was to compare the 54-week efficacy, immunogenicity, pharmacokinetics (PK) and safety of CT-P13 with RP in patients with ankylosing spondylitis (AS), with a focus on patient-reported outcomes (PROs).

**METHODS:** This was a multinational, double-blind, parallel-group study in patients with active AS. Participants were randomized (1:1) to receive CT-P13 (5 mg/kg) or RP (5 mg/kg) at weeks 0, 2, 6 and then every 8 weeks up to week 54. To assess responses, standardized assessment tools were used with an intention-to-treat analysis of observed data. Anti-drug antibodies (ADAs), PK parameters, and safety outcomes were also assessed.

**RESULTS:** Of 250 randomized patients (n=125 per group), 210 (84.0 %) completed 54 weeks of treatment, with similar completion rates between groups. At week 54, Assessment of Spondylo Arthritis international Society (ASAS)20 response, ASAS40 response and ASAS partial remission were comparable between treatment groups. Changes from baseline in PROs such as mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; CT-P13-3.1 versus RP -2.8), Bath Ankylosing Spondylitis Functional Index (BASFI; -2.9 versus -2.7), and Short Form Health Survey (SF-36) scores (9.26 versus 10.13 for physical component summary; 7.30 versus 6.54 for mental component summary) were similar between treatment groups. At 54 weeks, 19.5 % and 23.0 % of patients receiving CT-P13 and RP, respectively, had ADAs. All observed PK parameters of CT-P13 and RP, including maximum and minimum serum concentrations, were similar through 54 weeks. The influence of ADAs on PK was similar in the two treatment groups. Most adverse events were mild or moderate in severity. There was no notable difference between treatment groups in the incidence of adverse events, serious adverse events, infections and infusion-related reactions.

**CONCLUSIONS:** CT-P13 and RP have highly comparable efficacy (including PROs) and PK up to week 54. Over a 1-year period, CT-P13 was well tolerated and displayed a safety profile comparable to RP; no differences in immunogenicity were observed.

**TRIAL REGISTRATION:** ClinicalTrials.gov identifier: NCT01220518 . Registered 4 October 2010.


**BACKGROUND:** Tumour necrosis factor (TNF) inhibition and B-cell depletion are highly effective treatments for active rheumatoid arthritis, but so far no randomised controlled trials have directly compared their safety, efficacy, and cost-effectiveness. This study was done to test the hypothesis that using rituximab would be clinically non-
inferior and cheaper compared with TNF inhibitor treatment in biological-treatment naive patients with rheumatoid arthritis.

METHODS: This open-label, randomised controlled, non-inferiority trial enrolled patients with active, seropositive rheumatoid arthritis and an inadequate response to synthetic disease modifying anti-rheumatic drugs (DMARDs) from 35 rheumatology departments in the UK. Patients were randomly assigned 1:1 to the rituximab or TNF inhibitor groups with minimisation to account for methotrexate intolerance using a web-based randomisation system. Patients were given intravenous rituximab 1 g on days 1 and 15, and after 26 weeks if they responded to treatment but had persistent disease activity (28 joint count disease activity score [DAS28-ESR] >3.2; rituximab group) or a TNF inhibitor-adalimumab (40 mg subcutaneously every other week) or etanercept (50 mg per week subcutaneously) according to the patient's and rheumatologist's choice (TNF inhibitor group). Patients could switch treatment in the case of drug-related toxic effects or absence or loss of response. The primary outcome measure was the change in DAS28-ESR between 0 and 12 months in the per-protocol population of patients who were assigned to treatment and remained in follow-up to 1 year. We assessed safety in all patients who received at least one dose of study drug. We also assessed the cost-effectiveness of each strategy. The non-inferiority margin was specified as 0.6 DAS28-ESR units. This study is registered with ClinicalTrials.gov, number NCT01021735.

FINDINGS: Between April 6, 2009, and Nov 11, 2013, 295 patients were randomly assigned and given either rituximab (n=144) or TNF inhibitor (n=151) treatment. After 12 months, the change in DAS28-ESR for patients assigned to rituximab was -2.6 (SD 1.4) and TNF inhibitor was -2.4 (SD 1.5), with a difference within the prespecified non-inferiority margin of -0.19 (95% CI -0.51 to 0.13; p=0.24). The health-related costs associated with the rituximab strategy were lower than the TNF inhibitor strategy (9,405 vs 11,523 per patient, p<0.0001). 137 (95%) of 144 patients in the rituximab group and 143 (95%) of 151 patients in the TNF inhibitor group had adverse events. 37 serious adverse events occurred in patients receiving rituximab compared with 26 in patients receiving TNF inhibitors, of which 27 were deemed to be possibly, probably, or definitely related to the treatment (15 vs 12, p=0.5462). One patient in each group died during the study.

INTERPRETATION: Initial treatment with rituximab is non-inferior to initial TNF inhibitor treatment in patients seropositive for rheumatoid arthritis and naive to treatment with biologics, and is cost saving over 12 months.

FUNDING: Arthritis Research UK, Roche.

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OBJECTIVES: To demonstrate the pharmacokinetic equivalence of CT-P13 and its innovator infliximab (IFX) in Japanese patients with rheumatoid arthritis (RA), and to compare the efficacy and safety of these drugs, administered for 54 weeks.

METHODS: In a randomized, double-blind, parallel-group, multicenter study, 3 mg/kg of CT-P13 or IFX, in combination with methotrexate (MTX) (6-16 mg/week), was administered for 54 weeks to Japanese active RA patients with an inadequate response to MTX, to demonstrate the pharmacokinetic equivalence, based on the area under the curve
(AUC(tau)) (weeks 6-14) and C(max) (week 6) of these drugs, and to compare their efficacy and safety.

RESULTS: The CT-P13-to-IFX ratios (90% confidence intervals) of the geometric mean AUC(tau) and C(max) values in patients negative for antibodies to infliximab at week 14 were 111.62% (100.24-124.29%) and 104.09% (92.12-117.61%), respectively, demonstrating the pharmacokinetic equivalence of these drugs. In the full analysis set, CT-P13 and IFX showed comparable therapeutic effectiveness, as measured by the American College of Rheumatology, Disease Activity Score in 28 joints, the European League Against Rheumatism, and other efficacy criteria, at weeks 14 and 30. The incidence of adverse events was similar for these drugs.

CONCLUSION: CT-P13 and IFX, administered at a dose of 3 mg/kg in combination with MTX to active RA patients, were pharmacokinetically equivalent and comparable in efficacy and safety.


OBJECTIVE: To evaluate the efficacy and safety of secukinumab, a fully human antiinterleukin-17A monoclonal antibody, administered with an intravenous (IV) or subcutaneous (SC) loading regimen versus placebo, in patients with active rheumatoid arthritis (RA).

METHODS: In this phase II, double-blind, double-dummy, 52-week study (ClinicalTrials.gov NCT01359943), 221 patients with inadequate response to methotrexate were randomized (2:2:1) to secukinumab, IV loading 10 mg/kg at baseline, Weeks 2 and 4, then SC 150 mg every 4 weeks (n = 88); secukinumab SC loading 150 mg once weekly for 5 weeks, then every 4 weeks (n = 89); or a matching placebo (followed by secukinumab 150 mg every 4 weeks starting Week 16; n = 44). The primary endpoint was superior efficacy of pooled secukinumab versus placebo using American College of Rheumatology 20% response (ACR20) at Week 12.

RESULTS: The primary efficacy endpoint was not met: ACR20 response at Week 12 was 49.2% for pooled secukinumab versus 40.9% for placebo (p = 0.3559). These variables improved significantly with pooled secukinumab versus placebo at Week 12 (all p < 0.05): the 28-joint Disease Activity Score (DAS28), patient's and physician's global assessment of disease activity, patient's assessment of RA pain, and high-sensitivity C-reactive protein levels. Results of continuous efficacy outcomes were similar between the IV and SC loading regimens. The most frequent adverse events were infections, with similar rates across secukinumab and placebo.

CONCLUSION: Although the primary endpoint (ACR20) was not met, secukinumab demonstrated improved efficacy in reducing disease activity over placebo as measured by DAS28 and other secondary endpoints.


BACKGROUND: Tofacitinib is an oral Janus kinase inhibitor that is being investigated for psoriasis. Psoriasis impacts on physical and psychological well-being; improvements
in health-related quality of life (HRQoL) with etanercept in psoriasis are well
documented.

OBJECTIVE: To evaluate HRQoL with tofacitinib, vs. placebo or etanercept, in the Phase 3,
randomized, placebo-controlled, non-inferiority, Oral-treatment Psoriasis Trial (OPT)
Compare Study (NCT01241591).

METHODS: Adults with moderate to severe chronic plaque psoriasis were randomized 3:3:3:1
to tofacitinib 10 or 5 mg twice daily (BID), etanercept 50 mg twice weekly or placebo,
for 12 weeks. Patient-reported outcomes (PROs) included Dermatology Life Quality
Index (DLQI), Itch Severity Item and Patient Global Assessment of psoriasis.

RESULTS: At baseline, 83.4% (911/1092) of patients had a DLQI score ranging between 6 and
30, indicating a substantial burden of disease. By Week 12, 47.3%, 43.6% and 30.9% of
patients in the tofacitinib 10 mg BID, etanercept and tofacitinib 5 mg BID groups,
respectively, had a DLQI score of 0 or 1 (no effect of psoriasis on QoL) vs. 7.8% for
placebo (all P < 0.0001). Tofacitinib significantly reduced itch vs. placebo (P < 0.05 both
doses) and etanercept (P < 0.0001 both doses) within 1 day of starting treatment.
Furthermore, reductions in itch were greater with tofacitinib 10 mg BID, vs. etanercept,
at Weeks 2-12 (all time points P < 0.05). At Week 2, an Itch Severity Item score of 'little
or no itch' was more frequent with tofacitinib 10 mg (68.6%) vs. etanercept (57.4%) and
placebo (12.2%), and the PtGA response rate was significantly greater with tofacitinib 10
mg vs. placebo (P < 0.05).

CONCLUSION: Oral tofacitinib provided significant improvements across multiple PROs by
Week 12. Improvements with tofacitinib 10 mg BID were comparable to etanercept, and
improvements in itch were greater and more rapid with tofacitinib 10 mg BID.

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P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week
results from the PLANETRA study. Arthritis Research & Therapy. 18: 82.

BACKGROUND: CT-P13 (Remsima, Inflectra) is a biosimilar of the infliximab
reference product (RP; Remicade). The aim of this study was to compare the 54-week
efficacy, immunogenicity, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of
CT-P13 and RP in patients with active rheumatoid arthritis (RA).

METHODS: In this multinational phase III double-blind study, patients with active RA and an
inadequate response to methotrexate (MTX) were randomized (1:1) to receive CT-P13 (3
mg/kg) or RP (3 mg/kg) at weeks 0, 2, 6 and then every 8 weeks to week 54 in
combination with MTX (12.5-25 mg/week). Efficacy endpoints included American
College of Rheumatology (ACR)20, ACR50 and ACR70 response rates, Disease Activity
Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease
Activity Index (CDAI), European League Against Rheumatism (EULAR) response rates,
patient-reported outcomes and joint damage progression. Immunogenicity, safety and
PK/PD outcomes were also assessed.

RESULTS: Of 606 randomized patients, 455 (CT-P13 233, RP 222) were treated up to week 54.
At week 54, ACR20 response rate was highly similar between groups (CT-P13 74.7 %,
RP 71.3 %). ACR50 and ACR70 response rates were also comparable between groups
(CT-P13 43.6 % and 21.3 %, respectively; RP 43.1 % and 19.9 %, respectively). DAS28, SDAI and CDAI decreased from baseline to week 54 to a similar extent with CT-P13 and RP. Radiographic progression measured by Sharp scores as modified by van der Heijde was also comparable. With both treatments, patient assessments of pain, disease activity and physical ability, as well as mean scores on the Medical Outcomes Study Short Form Health Survey (SF-36), improved markedly at week 14 and remained stable thereafter up to week 54. The proportion of patients positive for antidrug antibodies at week 54 was similar between the two groups: 41.1 % and 36.0 % with CT-P13 and RP, respectively. CT-P13 was well tolerated and had a similar safety profile to RP. PK/PD results were also comparable between CT-P13 and RP.

CONCLUSIONS: CT-P13 and RP were comparable in terms of efficacy (including radiographic progression), immunogenicity and PK/PD up to week 54. The safety profile of CT-P13 was also similar to that of RP.