IQWiG Reports – Commission No. A18-51

Tofacitinib (psoriatic arthritis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Tofacitinib (Psoriasis Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Tofacitinib (psoriatic arthritis) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
24 August 2018

Internal Commission No.:
A18-51

Address of publisher:
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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: tofacitinib, arthritis – psoriatic, benefit assessment, NCT01877668

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tofacitinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 24 August 2018.

Research question

The aim of this report is to assess the added benefit of tofacitinib in combination with methotrexate in comparison with the appropriate comparator therapy (ACT) in adult patients with active psoriatic arthritis who did not adequately respond to or did not tolerate prior disease-modifying antirheumatic drug (DMARD) therapy.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2[2]: Research questions of the benefit assessment of tofacitinib

Research question	Indication	ACT[a]
1	Patients with active psoriatic arthritis who failed to adequately respond to or did not tolerate prior disease-modifying antirheumatic drug (DMARD) therapy[b]	TNF-alpha inhibitor (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab), if applicable, in combination with methotrexate
2	Patients with active psoriatic arthritis who failed to adequately respond to or did not tolerate previous biological disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or secukinumab or ustekinumab), if applicable, in combination with methotrexate
a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. b: The patient population considered for research question 1 was bDMARD-naïve patients. ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor		

In this assessment, the following terms are used for the patient populations of the two research questions:

- Research question 1: bDMARD-naïve patients with active psoriatic arthritis who did not respond adequately to prior DMARD therapy.
- Research question 2: Patients with active psoriatic arthritis who did not respond adequately to prior bDMARD therapy

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

The company stated that it followed the G-BA's specifications for research question 1 and chose adalimumab from the presented options. However, the company failed to mention that – in case of combination therapy with a TNF (tumour necrosis factor) alpha inhibitor – methotrexate is the only combination partner of adalimumab.

For research question 2, the company did not select an ACT. It justified this approach by the fact that no study was presented to prove added benefit.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving the added benefit.

Results

Research question 1: bDMARD-naïve patients with active psoriatic arthritis who failed to respond adequately to prior DMARD therapy.

For bDMARD-naïve patients with active psoriatic arthritis who failed to respond adequately to prior DMARD therapy, the company presented the randomized controlled trial OPAL BROADEN.

OPAL BROADEN study

Included were adult patients with active psoriatic arthritis and an inadequate response to at least 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD) due to a lack of effectiveness or toxicity or inadequate tolerance and without prior TNF inhibitor therapy. In total, 422 patients were randomly allocated to 5 study arms. Only the study arms tofacitinib 5 mg (dosage specified in the summary of product characteristics [SPC]) and adalimumab 40 mg (specified ACT) are relevant for this assessment. The study medication was administered as an add-on to the existing stable csDMARD therapy. In the study, the csDMARD was administered as an add-on to the study medication until the completion of the study.

Unsuitability of the data of the OPAL BROADEN study presented by the company

To support an added benefit, the company used the results of all patients of both treatment arms. This approach is inappropriate since a relevant percentage of the patients in the comparator arm did not receive the ACT specified by the G-BA.

In accordance with the specified ACT, methotrexate is the only member of the group of TNF-alpha inhibitors to be used as the potential combination partner of adalimumab. Furthermore, according to the SPC, tofacitinib is approved exclusively in combination with methotrexate.

In the OPAL BROADEN study, however, patients in the tofacitinib or adalimumab arms received not only methotrexate, but also other DMARDs as add-on therapy. The latter particularly included sulfasalazine and leflunomide.

Contrary to the specified ACT, in the adalimumab arm, 24.5% of patients received sulfasalazine, leflunomide, or hydroxychloroquine as add-on therapy. Only 75.5% of patients received methotrexate add-on therapy. Hence, fewer than 80% of patients received adalimumab in accordance with the specified ACT, and consequently, no reliable conclusion can be drawn on added benefit on the basis of the presented data for the target population.

In the tofacitinib arm, more than 80% of patients met the inclusion criterion regarding the experimental intervention. In total, 86% of patients received methotrexate as the combination partner, as approved.

Overall, due to the failure to implement the ACT in > 20% of patients in the comparator arm, the data presented by the company for all patients of the tofacitinib and adalimumab arms were insufficient for drawing reliable conclusions on the added benefit of tofacitinib in comparison with the ACT. This would require comprehensive analyses on all patient-relevant outcomes for the relevant subpopulation of patients who received tofacitinib or adalimumab in combination with methotrexate.

Research question 2: Patients with active psoriatic arthritis who did not respond adequately to prior bDMARD therapy

No data are available for assessing the added benefit of tofacitinib in comparison with the ACT in patients with active psoriatic arthritis who did not respond adequately to or did not tolerate prior bDMARD therapy. Consequently, there is no hint of added benefit of tofacitinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of tofacitinib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Tofacitinib – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Patients with active psoriatic arthritis who failed to adequately respond to or did not tolerate prior disease-modifying antirheumatic drug (DMARD) therapy[b]	TNF-alpha inhibitor (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab), if applicable, in combination with methotrexate	Added benefit not proven
Patients with active psoriatic arthritis who failed to adequately respond to or did not tolerate previous biological disease-modifying antirheumatic drug (bDMARD) therapy	Switch to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or secukinumab or ustekinumab), if applicable, in combination with methotrexate	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b: The patient population considered for research question 1 was bDMARD-naïve patients.
ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The G-BA decides on the added benefit.

Note:

An addendum (A19-03) to dossier assessment A18-51 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-51-tofacitinib-psoriatic-arthritis-benefit-assessment-according-to-35a-social-code-book-v.10484.html.