Use of a risk characterisation approach to contextualise the safety profile of new rheumatoid arthritis treatments: a case study using tofacitinib

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Abstract Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). To characterise the relative safety profile of tofacitinib to biologic disease-modifying antirheumatic drugs (bDMARDs), the accrued patient-years (pt-yrs) of exposure needed in an RA clinical trial programme to detect a potential increase in risk of specific adverse events (AEs) was determined. This case study/framework was constructed on the pt-yrs’ accrual within pooled phase (P)1, P2 and P3, as well as long-term extension, studies of tofacitinib in RA (March 2015 data-cut) and published AE incidence rates for bDMARDs. Sample size calculations were based on a Poisson distribution to estimate pt-yrs’ exposure required for 90 % probability that the lower bound of the 95 % confidence interval for tofacitinib/bDMARD would be >1, assuming that tofacitinib rates were 1.2×/1.5×/2.0× greater than comparator rates. AE rates for bDMARDs were derived from sources intended to optimise similarity with the tofacitinib database in terms of baseline characteristics, study duration and follow-up. Based on the tofacitinib exposure accrued (19,406 pt-yrs), data were sufficient (90 % probability) to detect potential differences over external bDMARD comparator rates in serious infections (≥1.2×), malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, major adverse cardiovascular events (MACE) and lymphoma (each ≥1.5×), as well as opportunistic infections and gastrointestinal perforations (≥2×), should they exist. This risk characterisation approach can support the comparative safety of new RA medications. To date, tofacitinib safety appears similar to approved published data from bDMARDs with respect to serious infections, malignancies (excluding NMSC), NMSC, MACE, lymphoma, opportunistic infections and gastrointestinal perforations.

Keywords Exposure · Rheumatoid arthritis · Safety · Tofacitinib · Tumour necrosis factor inhibitors

Introduction

Safety data collected during the development of new rheumatoid arthritis (RA) therapies are generally derived from randomised controlled trials (RCTs) and long-term extension (LTE) studies. Individual RCTs typically include small patient numbers and limited treatment periods [1, 2]. Control treatment duration may limit the exposure available to derive relative safety measures with concurrent internal controls, particularly for events of low frequency or long latency. Although LTE studies are conducted over longer treatment periods, many of these typically do not include a comparator arm, are open-label and may lack generalisability due to possible selection biases [2]; such factors complicate comparisons with controls.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib clinical efficacy and safety have been demonstrated in phase (P)3 and LTE studies (Supplementary...
Materials and methods

External comparator populations

For this analysis, the Curtis et al. methodology was applied [1]. bDMARDs were chosen for comparison with tofacitinib, and incidence rates (IRs) for AEs of interest in patients with moderate to severe RA were obtained to determine the tofacitinib exposure needed to detect a potential increased risk of the following AEs: serious infection events (SIEs), all malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC, major adverse cardiovascular events (MACE), opportunistic infections (OIs), lymphoma and gastrointestinal (GI) perforations. These AEs were selected by the study team as important potential or identified risks for RA patients that were both clinically relevant and feasible for study under the methodological framework. For instance, although pregnancy safety outcomes were of interest, there were no adequately powered, well-controlled studies of pregnant women treated with tofacitinib. For the outcomes of interest, data from multiple sources (e.g. observational studies, RCTs, meta-analyses) were used and data sources were focussed on defining and optimising comparability with the tofacitinib clinical trial programme (Table 1; Supplementary Material).

Tofacitinib clinical trial population

The tofacitinib clinical trial RA population included patients from two P1 studies, nine P2 RCTs, six P3 RCTs and two open-label LTE studies (Supplementary Material). One LTE study was ongoing at the time of analysis (March 2015 data cut; unlocked).

Analysis

Background rates of AEs were derived from external bDMARD comparator populations, as described previously. IRs were expressed as the number of unique patients with events per 100 pt-yrs’ exposure, assuming a constant hazard over time. Sample size calculations were based on a Poisson distribution to estimate the minimum pt-yrs’ exposure needed to have 90 % power to detect that the lower bound of the CI of tofacitinib/bDMARD would be >1, assuming that the true tofacitinib IRs were 1.2×, 1.5× or 2.0× greater than bDMARD IRs; multiplier thresholds were based on clinical relevance and 1.5× was used by Curtis et al., as agreed upon with the FDA for characterising tocilizumab safety [1].

Accrued exposure data collected during tofacitinib studies (P123LTE) were pooled for analysis. The number of pt-yrs’ exposure within the pooled dataset was compared with the calculated minimum tofacitinib exposure to detect a 1.2×, 1.5× or 2.0× increase in risk over external bDMARD comparator populations for each AE.

Results

As of March 2015, 19,406 pt-yrs’ tofacitinib exposures (all doses) were accrued from 6194 patients across the P123LTE database. IRs for AEs of interest in the external bDMARD comparator populations, with similar characteristics to patients enrolled in the tofacitinib clinical trial programme, are shown in Table 1. A nomogram was developed to estimate the number of pt-yrs’ tofacitinib exposure required to detect increases in AEs of various frequencies (Fig. 1).

Based on 19,406 pt-yrs’ tofacitinib exposure, sufficient data were available to detect potential increases over estimated background bDMARD IRs in SIEs (≥1.2×), malignancies (excluding NMSC), NMSC, MACE and lymphoma (each ≥1.5), should they exist. Given the rarity of OIs and GI perforations reported in RA populations, the accrued pt-yrs’ exposure allows for the detection of a potential two-fold increase with tofacitinib relative to bDMARD IRs.

Discussion

A robust clinical trial safety database is important for the risk/benefit assessment of a new molecular entity (NME) and should meet regulator recommendations on the extent of population exposure to assess clinical safety [19]. At the time of initial registration, RA clinical trials predominantly focussed on comparisons with placebo, with pooling across trials to achieve the necessary extent of exposure. However, as the number of effective RA therapies has increased and ethical considerations have further limited the length of placebo...
exposure in contemporary clinical trial programmes, interest has shifted to characterising the safety profile of new medications versus other active medications rather than placebo.

Modern development programmes generally include head-to-head or active comparator trials, with the primary intent of benchmarking the efficacy of NME. While the duration of active comparator trials is typically longer compared with placebo-controlled trials and is not as restrictive in terms of duration of exposure, logistical considerations, including sample size, study duration and event frequency, continue to limit the ability to draw precise comparisons for events with low frequency or long latency.

Furthermore, the challenge remains as to how to determine a priori how much data constitutes a sufficiently large safety database in such a clinical trial programme. Due to these difficulties, there is utility in alternative methods to compare the evidence of safety events between active therapies. Our approach, which focussed on confirmation that the minimum drug exposure within the tofacitinib clinical trial programme has been achieved to confidently ascertain whether AE rates are higher than other available therapies, may improve the utility of other clinical trial programme databases.

The data suggest that tofacitinib exposure from the clinical programme is sufficient to detect possible risk differences

| Event | External bDMARD comparator population | IR reported for external bDMARD comparator population per 100 pt-yrs<sup>a</sup> | Follow-up exposure (pt-yrs) to tofacitinib required to detect an assumed increased risk relative to bDMARDs with 90 % power<sup>b</sup> |
|-------|--------------------------------------|---------------------------------|--------------------------------------------------|
| SIE   | Systematic review/clinical trial meta-analysis [12] | Point estimate 4.90 | 6151 1076 311 |
|       |                                      | Lower 95 % CI 4.41            | 6568 1230 348 |
|       |                                      | Upper 95 % CI 5.44            | 5384 985 296 |
| Malignancies (excluding NMSC) | Clinical trials meta-analysis (Pfizer Inc 2015, data on file) | Point estimate 0.95 | 30,945 5704 1699 |
|       |                                      | Lower 95 % CI 0.79            | 38,165 6872 2004 |
|       |                                      | Upper 95 % CI 1.14            | 25,734 4743 1413 |
| NMSC  | Published systematic review/meta-analysis of malignancies from observational studies/clinical trials [13] | 0.35 84,544 15,241 4349 |
|       | Observational studies literature review (Pfizer Inc 2015, data on file) | Low 0.21 137,762 25,444 7263 |
|       |                                      | High 1.34 22,366 3933 1146   |
| MACE  | Corona TNFi cohort (Pfizer Inc 2013, data on file) | 0.54 54,684 10,084 2942   |
| OI    | Based on published long-term follow-up data of patients with active RA treated with adalimumab [14]; published literature review of infections and bDMARD therapy among patients with RA [15] | 0.25<sup>c</sup> 118,491 21,363 6098 |
| Lymphoma | Observational studies literature review (Pfizer Inc 2015, data on file) | Low 0.019 1,562,987 281,872 80,494 |
|       |                                      | High 0.34 87,040 15,691 4478 |
| GI perforation | Published claims database analysis [16, 17] | 0.13 228,162 39,228 11,746 |
|       |                                      | Lower 95 % CI 0.08            | 370,964 66,896 19,101 |
|       |                                      | Upper 95 % CI 0.19            | 156,011 28,129 8030 |
|       | Published RABBIT registry data<sup>d</sup> [18] | High 0.066 449,723 77,326 22,080 |
|       | Observational studies literature review (Pfizer Inc 2015, data on file) | Low 0.05 593,737 107,072 30,575 |
|       |                                      | High 0.19 156,011 28,129 8030 |

Shaded cells highlight events that have accrued the needed tofacitinib exposure for the detection of respective 1.2×, 1.5× or 2.0×-fold increased risk, should they occur, based upon trial data current through March 2015.

*bdMARD* biologic disease-modifying antirheumatic drug, *CI* confidence interval, *Corrorna* Consortium of Rheumatology Researchers of North America, *EU* European, *GI* gastrointestinal, *IR* incidence rate, *MACE* major adverse cardiovascular event, *ND* not determined, *NMSC* non-melanoma skin cancer, *OI* opportunistic infection, *pt-yrs* patient years, *RA* rheumatoid arthritis, *RABBIT* Rheumatoid Arthritis Observational Biological Therapy Register, *SIE* serious infection event, *TNFi* tumour necrosis factor inhibitor

<sup>a</sup>Low and high refer to the lowest and highest IR values, respectively, from a range of reported values

<sup>b</sup>The estimated tofacitinib exposure by April 2015 within the RA clinical programme is 19,406 pt-yrs

<sup>c</sup>No CI available

<sup>d</sup>The low value was 0 (golimumab data); therefore, exposure data could not be calculated
from bDMARDs of $\geq 1.2$–$1.5 \times$ for several AEs of interest; however, for OIs and GI perforations, only risk differences of $\geq 2 \times$ could be detected due to the lower frequency of these events within the available data sources. This reflects the inherent limitation of event frequency in precisely comparing such events. For such rare events, the potential risk differences that can be detected using this method may be considered insufficient to fully inform risk/benefit assessments. This limitation highlights the important role of observational studies, conducted in larger and more diverse patient populations, to assess the relative frequency of such events and those with long latency periods. Such characterisation can be achieved through prospective active surveillance within register frameworks and routine pharmacovigilance surveillance within the clinical practice setting. Ideally, one could potentially pool clinical trial data, continued by real-world observation, to provide maximal person-time follow-up.

In this analysis, limitations were introduced from the data sources used. The paucity of data available from clinical trials for some AEs of interest required the use of observational data sources and meta-analyses to provide the necessary IRs for these events in cohorts of patients receiving bDMARDs. The addition of observational sources, rather than only clinical trial data, increased the breadth of IRs available and may have influenced the sensitivity to detect a potential increased risk with tofacitinib relative to bDMARDs. These data, while valuable, introduce a wider range of patient characteristics and risk factors representative of clinical practice versus trial-specific inclusion/exclusion criteria, as well as heterogeneity in case definitions and the methods of outcome ascertainment. To address these limitations, where possible, bDMARD populations were selected to optimise similarity of comparisons with the tofacitinib clinical trial database and provide a conservative range of IRs.

A similar analytic approach was used for tocilizumab for regulatory purposes, where the number of tocilizumab-exposed pt-yrs needed to detect a $\geq 50 \%$ increase in risk for key safety events versus a bDMARD population (90 % power) was determined. The overall methodologies were similar, except that within this case example, additional efforts to ‘harmonise’ the comparator patient populations were made, and all tofacitinib-related person-time was accrued within the clinical trial setting versus the combination of clinical trial and person-time estimates based on post-marketing exposure for tocilizumab [1].

The methodology described here for the tofacitinib clinical trial programme provides clinicians and experts in pharmacovigilance with an alternative way to gain perspective on the pt-yrs’ exposure required to evaluate differences in safety events of interest relative to comparator therapies. The AEs selected for this analysis were those identified by the study team as the most clinically relevant potential risks for RA patients. However, the methodology described herein could be applied to evaluate the relative risk of other safety outcomes of interest, such as abnormal laboratory test results associated with clinically relevant outcomes, which have been reported elsewhere in tofacitinib-treated RA patients [20, 21].

This approach could support the assessment of comparative safety outcomes for new RA medications. Based on our dataset, a nomogram was developed to estimate the number of pt-yrs’ tofacitinib exposure required to detect potential increases in risk versus bDMARDs, as a tool that could be more broadly applied in the design of long-term safety clinical trials and real-world safety comparisons. A 90 % power for

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**Fig. 1** Nomogram showing the minimum amount of tofacitinib exposure (pt-yrs) required to detect a significant difference of 1.5× and 2.0× versus a bDMARD comparator in relation to example background event rates. As of March 2015. IRs for AEs of interest are based on estimated values from the data presented in Table 1. AE adverse event, bDMARD biologic disease-modifying antirheumatic drug, GI gastrointestinal, IR incidence rate, MACE major adverse cardiovascular event, NMSC non-melanoma skin cancer, pt-yrs patient-years, OI opportunistic infection, SIE serious infection event.
exposure calculations was selected to ensure a higher chance of detecting potential differences rather than a lower threshold. Consequently, the tofacitinib exposure calculated represents a conservative estimate of the total pt-ys follow-up.

Although our case study used a superiority hypothesis for safety events, non-inferiority testing would result in similar exposure sample size cutoffs for each AE of interest within non-inferiority margin set at the same values, as described for each event within the nomogram (1.5×, 2.0×). In non-inferiority testing, if the upper bound of 95% CI based on the observed tofacitinib rate was <1.5× and 2.0× of bDMARD comparator rates, then 1.5× and 2.0× risks could be excluded. Therefore, regardless of superiority test (to detect assumed difference) or non-inferiority test (to exclude certain difference), similar inference could be drawn; an assumption of the analysis was that the IR of AEs for bDMARDs were constant over time. Whether this is a valid assumption can be tested as accumulating data allows.

The tofacitinib data are derived entirely from clinical trial data sources. Given that >55,000 patients worldwide have received tofacitinib as of May 2015 (data on file), in post-marketing experience, additional perspective for the evaluation of rare events in this more heterogeneous real-world patient and prospective active surveillance using registries is ongoing to fully define the risks associated with therapy. Future safety analyses might also include alternative comparator therapies within such registries, which would complement both the comparative clinical trials and the methods described here. Comparative safety outcome trials (NCT02092467/A3921133) are underway, but data will not be available in the near future. The creation of a safety data repository of blinded patient-level data to permit cross-comparison between existing therapies and new medications could allow for standardisation of cohort and outcome definitions and better comparability for key subgroups. This approach has been preliminarily successful in trying to harmonise international comparisons between observational RA registries [22, 23]. Additionally, a Bayesian approach, incorporating the latest safety estimates, could be considered. The current estimated sample size ignores the event rates associated with tofacitinib; this analytic framework is suitable for planning how much exposure data might be needed before actual tofacitinib rates are available.

To conclude, our risk characterisation approach represents an indirect method to contextualise the safety profile of newly introduced RA medications versus established therapies, and provides clinicians and regulatory authorities with relevant context to inform labelling and treatment choices for RA patients. To date, the safety of tofacitinib appears similar to approved published data from bDMARDs with respect to SIEs, all malignancies (excluding NMSC), NMSC, MACE, OIs, lymphoma and GI perforations.

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Compliance with ethical standards All tofacitinib studies were approved by the Institutional Review Boards (IRBs) and/or Independent Ethics Committees of each investigational centre or a central IRB. The studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

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Conflict of interest JC has received grant or research support from Pfizer Inc for unrelated work. AA was a shareholder and employee of Pfizer Inc at the time the analyses were performed. YC, SK, RZ, SS, CC and JG are shareholders and employees of Pfizer Inc.

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Wyman BT, Gruben D, Benda B, Wallenstein G, Krishnaswami S, Zwillich SH, Bradley JD, Connell CA. ORAL Scan Investigators (2013) Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 65:559–570

8. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, Foretova S, Zwillich SH, Gruben D, Koncz T, Wallenstein GV, Krishnaswami S, Bradley JD, Wilkinson B. Standard Investigators ORAL (2012) Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 367:508–519

9. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, Nduaka CI, Benda B, Gruben D, Nakamura H, Komuro Y, Zwillich SH, Wang L, Riese RJ (2014) Safety and efficacy of tofacitinib, an oral Janus kinase Inhibitor, in the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol 41:837–852

10. Wollenhaupt J, Silverfield J, Lee EB, Terry K, Kwok K, Lazariciu I, Nduaka C, Connell CA, DeMasi R, Wang L (2015) Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: safety and clinical and radiographic efficacy in open-label, long-term extension studies over 7 years. Arthritis Rheumatol 67(Suppl 10): Abstract 1645

11. Food and Drug Administration (2015) BLA 125276/S049 Medical review(s). pp 1–75. http://www.accessdata.fda.gov/drugsatfda_docs/bla/2012/125276Orig1s049MedR.pdf

12. Strand V, Ahadieh S, French J, Geier J, Krishnaswami K, Menon S, Checchio T, Tensfeldt T, Hoffman E, Riese R, Boy M, Gómez-Reino J (2015) Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther 17:362

13. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R, Walsh C, Lawson R, Reynolds A, Emery P (2011) Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 70:1895–1904

14. Keystone EC, van der Heijde D, Kavanaugh A, Kupper H, Liu S, Guerette B, Mozaffarian N (2013) Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. J Rheumatol 40: 1487–1497

15. Winthrop KL (2012) Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. Rheum Dis Clin North Am 38:727–745

16. Gout T, Ostor AJ, Nisar MK (2011) Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Clin Rheumatol 30:1471–1474

17. van Vollenhoven RF, Ronald F, Keystone E, Edward C, Furie R, Blesch A, Wang C, Curtis JR (2009) Gastrointestinal safety in patients with rheumatoid arthritis treated with tocilizumab: data from Roche clinical trials. Arthritis Rheum 60(Suppl 10):Abstract 1613

18. Strangfeld A, Richter A, Herzer P, Rockwitz K, Demary W, Aringer M, Zink A, Listing J (2015) Risk for lower intestinal perforations in RA patients treated with tocilizumab in comparison to treatment with TNF inhibitors, rituximab, abatacept or conventional synthetic DMARDs. Arthritis Rheum 67(Suppl 10):Abstract 2051

19. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1994) The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions: E1. pp. 1–3 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

20. Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, Boy M, Geier J, Luo Z, Zuckerman A, Riese R (2016) Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. Semin Arthritis Rheum. doi:10.1016/j.semarthrit.2016.03.004

21. Isaacs JD, Zuckerman A, Krishnaswami S, Nduaka C, Lan S, Hutmacher MM, Boy MG, Kowalski K, Menon S, Riese R (2014) Changes in serum creatinine in patients with active rheumatoid arthritis treated with tofacitinib: results from clinical trials. Arthritis Res Ther 16:R158

22. Nyberg F, Askling J, Berglund N, Franzén S, Ho M, Holmqvist M, Horne L, Lampl K, Michaud K, Pappas DA, Reed G, Symmons D, Tanaka E, Tran TN, Westerhamn SM, Wesby-van SE, Yamanaka H, Greenberg JD (2015) Using epidemiological registry data to provide background rates as context for adverse events in a rheumatoid arthritis drug development program: a coordinated approach. Pharmacoepidemiol Drug Saf 24:1121–1132

23. Verstappen SM, Askling J, Berglund N, Franzén S, Frisell T, Garwood C, Greenberg JD, Holmqvist M, Horne L, Lampl K, Michaud K, Nyberg F, Pappas DA, Reed G, Symmons DP, Tanaka E, Tran TN, Yamanaka H, Ho M (2015) Methodological challenges when comparing demographic and clinical characteristics of international observational registries. Arthritis Care Res (Hoboken) 67:1637–1645