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Clinical science

Efficacy of subcutaneous *vs* intravenous infliximab in rheumatoid arthritis: a post-hoc analysis of a randomized phase III trial

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Abstract

Objectives: The primary endpoint of the pivotal phase III study of infliximab (IFX) s.c. demonstrated non-inferiority of s.c. to i.v. IFX, based on 28-joint DAS-CRP (DAS28-CRP) improvement at week (W) 22 (NCT03147248). This post-hoc analysis investigated whether numerical differences in efficacy outcomes at W30/54 were statistically significant, using conservative imputation methods.

Methods: Patients with active RA and inadequate response to MTX received IFX i.v. 3 mg/kg at W0 and W2 (induction) and were randomized (1:1) to IFX s.c. 120 mg every 2 weeks or i.v. 3 mg/kg every 8 weeks thereafter (maintenance). Patients randomized to IFX i.v. switched to IFX s.c. from W30–54. This post-hoc analysis compared efficacy outcomes for s.c. and i.v. groups pre-switch (W30) and post-switch (W54) using last observation carried forward (LOCF) and non-responder imputation (NRI) methods.

Results: Of 343 randomized patients, 165 (IFX s.c.) and 174 (IFX i.v.) were analysed. At W30, significantly improved outcomes were identified with s.c. *vs* i.v. IFX for DAS28-CRP/DAS28-ESR/Clinical Disease Activity Index (CDAI)/Simplified Disease Activity Index (SDAI) scores (LOCF); ACR/good EULAR responses, DAS28-CRP/Boolean remission, and DAS28-CRP/DAS28-ESR/CDAI/SDAI low disease activity and remission (LOCF and/or NRI); and minimal clinically important difference in HAQ score (LOCF and NRI). After switching to IFX s.c. from IFX i.v., fewer significant between-group differences were identified at W54.

Conclusion: IFX s.c. showed improved efficacy at W30 compared with IFX i.v., and the reduced between-group difference in efficacy outcomes at W54 after switching supports the results suggesting benefits of IFX s.c. compared with IFX i.v. at W30.

Trial registration: ClincialTrials.gov, http://clinicaltrials.gov, NCT03147248, https://clinicaltrials.gov/ct2/show/NCT03147248.

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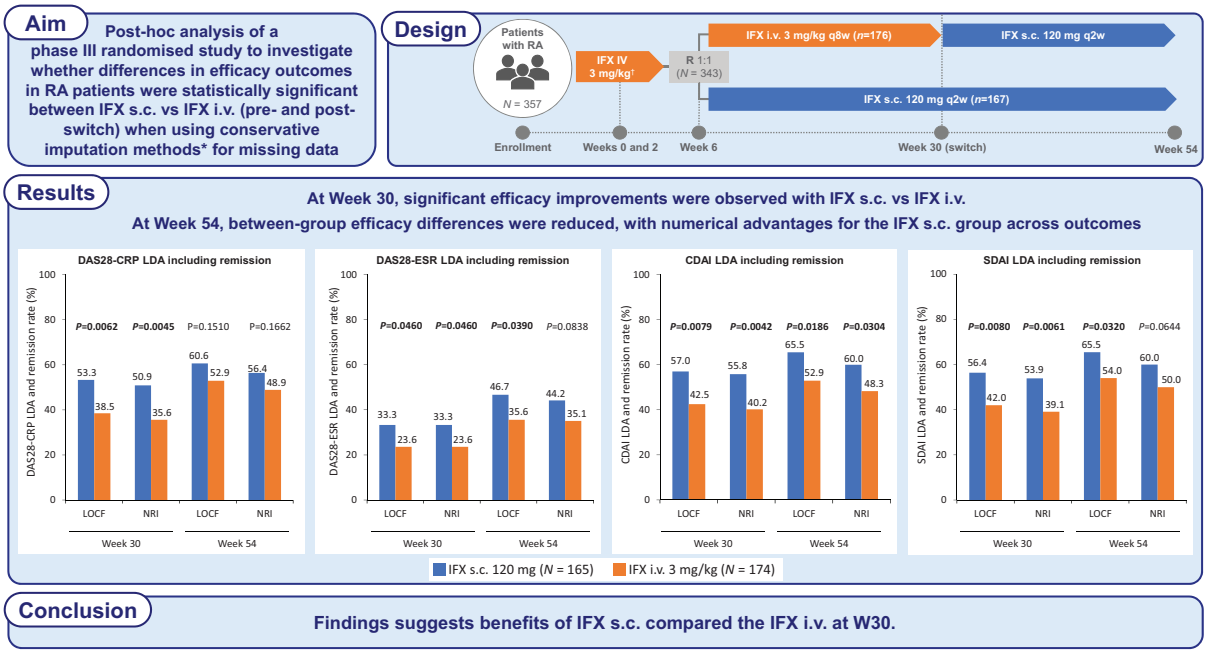
Graphical abstract



*LOCF and NRI; †During the i.v. dose-loading phase, IFX i.v. 3 mg/kg was administered via 2-hour i.v. infusion at Weeks 0 and 2
CDAI, Clinical Disease Activity Index; DAS28, disease activity score in 28 joints; IFX, infliximab; i.v., intravenous; LDA, low disease activity; LOCF, last observation carried forward; NRI, non-responder imputation; qnw, every *n* weeks; R, randomisation; RA, rheumatoid arthritis; s.c., subcutaneous; SDAI, Simplified Disease Activity Index

Keywords: RA, clinical trials and methods, inflammation, biologic therapies, immunosuppressants

Rheumatology key messages

- Infliximab s.c. was associated with improved efficacy *vs* infliximab i.v. in patients with RA.
- Conservative imputation methods showed significant efficacy improvements with infliximab s.c. *vs* i.v. at Week 30.
- Between-group efficacy differences decreased after patients switched from infliximab i.v. to s.c., suggesting a switching benefit.

Introduction

A s.c. formulation of infliximab (IFX), CT-P13 s.c., received European Union approval for the treatment of adult RA in 2019; all other indications for the s.c. formulation of infliximab were approved in 2020 [1]. Approval of IFX s.c. followed the pivotal phase III randomized controlled study [2] that demonstrated that IFX s.c., in combination with MTX, was non-inferior to IFX i.v. in patients with active RA and an inadequate response to MTX [3]. While IFX s.c. and IFX i.v. showed similar efficacy up to week (W) 22, numerically improved efficacy was observed with IFX s.c. *vs* IFX i.v. at W30 in a number of outcomes [3]. Patients receiving IFX i.v. switched to IFX s.c. at W30, and at the end of the maintenance period (W54), and efficacy findings were similar between groups [3].

It is important to further assess whether there are differences in efficacy between the i.v. and s.c. formulations of IFX. The potentially improved efficacy identified with CT-P13 s.c. *vs* CT-P13 i.v. at W30 could be of particular relevance to the management of patients with RA; per EULAR recommendations, if the treatment goal is not reached after W30, the treatment strategy should be adjusted, reflecting the critical importance of rapidly achieving therapeutic goals [4].

Although the pivotal phase III study identified numerical differences in efficacy outcomes between groups favouring IFX s.c., the possibility has been raised that these favourable results may have been caused by the early dropout of many patients treated with IFX s.c. for reasons of worsening disease or insufficient effectiveness.

Therefore, a post-hoc analysis of the pivotal study data was conducted to investigate whether numerical differences between IFX s.c. and IFX i.v. at W30 and W54 were statistically significant when conservative imputation methods for missing data were applied.

Methods

Study design and procedures

A post-hoc analysis was conducted using data from the pivotal, randomized, double-blind, multicentre, phase III study of IFX s.c. (NCT03147248) [3]. Detailed information regarding study centres and study design is reported in the primary publication [3] and summarized in Supplementary Fig. S1, available at *Rheumatology* online. Briefly, following an i.v. dose-loading phase (IFX i.v. 3 mg/kg via 2-h i.v. infusion at W0 and W2), patients were randomized (1:1) at W6 to receive IFX s.c., 120 mg every 2 weeks (q2w), or a 2-h i.v. infusion of IFX i.v., 3 mg/kg every 8 weeks. Double-dummy placebos were used to maintain blinding until W30, when patients receiving IFX i.v. were switched to IFX s.c. 120 mg q2w until

W54. All patients received MTX (12.5–25 mg/week; 10–25 mg/week in the Republic of Korea) and folic acid (≥5 mg/week) throughout the study.

As previously reported [3], the study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Prior to study initiation, the study protocol was reviewed and approved by the independent ethics committee/institutional review board at each site. All participants provided written informed consent.

Target population

Full eligibility criteria are reported in the primary publication [3]. Briefly, participants were adults (aged 18–75 years) with active RA for ≥30 weeks prior to first administration of study drug (day 0), had an inadequate response to ≥3 months of MTX, and had received a stable dose of MTX (12.5–25 mg/week; 10–25 mg/week in the Republic of Korea) for ≥4 weeks prior to day 0. Patients fulfilled the 2010 ACR/EULAR RA classification criteria [5], and active RA was defined by the presence of ≥6 swollen joints (28-joint count), ≥6 tender joints (28-joint count), and a serum CRP concentration of >0.6 mg/dl. Individuals who had previously received a biologic agent for RA and/or a TNF inhibitor for another disease were excluded.

Study endpoints

Primary and secondary study endpoints were previously reported [3]. Efficacy outcomes assessed at W30 (~6 months) and W54 (~12 months) in the present post-hoc analysis comprised mean and change from baseline in DAS28-CRP, DAS28-ESR, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI); ACR response rate; EULAR response rate; remission and low disease activity (LDA), including remission rate based on DAS28-CRP, DAS28-ESR, CDAI, and SDAI; Boolean remission rate; ACR/EULAR remission rate; and the proportion of patients achieving a minimal clinically important difference (MCID) in the HAQ estimate of physical ability score [6]. Supplementary Table S1, available at *Rheumatology* online, presents the definitions for the endpoints assessed in the current analysis.

Statistical analyses

Sample size calculations were previously described [3]. All analyses were conducted in the efficacy population (see Supplementary material available at *Rheumatology* online for population details). Missing data for each visit were imputed using the last observation carried forward (LOCF) method for continuous and binary endpoints and non-responder imputation (NRI) for binary endpoints (see Supplementary material available at *Rheumatology* online). Statistical significance was determined based on a two-sided significance level of 5%. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient disposition

Patients were enrolled to the IFX s.c. pivotal study from 30 October 2017, and the last patient's last study centre visit was on 15 April 2019 [3]. Of the 357 patients enrolled, 343 were randomized to receive IFX s.c. ($N = 167$) or IFX i.v. ($N = 176$) at W6. All patients received IFX s.c. treatment from W30 (~6 months) to W54 (~12 months). This post-hoc analysis included all patients in the efficacy population [IFX s.c. ($N = 165$); IFX i.v. ($N = 174$)], of whom 284 [IFX s.c. ($N = 141$), IFX i.v. ($N = 143$)] completed the study. As previously reported [3], patient demographics and disease characteristics were balanced between groups at W6 (all-randomized population).

DAS28-CRP, DAS28-ESR, CDAI, and SDAI scores

At W30, mean DAS28-CRP and DAS28-ESR scores were significantly lower with IFX s.c. *vs* IFX i.v. (LOCF: $P < 0.05$; Fig. 1A–B). Mean changes from baseline were also significantly improved with IFX s.c. *vs* IFX i.v. ($P < 0.05$ for both DAS28-CRP and DAS28-ESR). Mean DAS28-CRP and DAS28-ESR scores were maintained between W30 and W54 with IFX s.c., with between-group differences reduced at W54 ($P > 0.05$). However, the IFX s.c. group maintained a significantly greater change from baseline in both DAS28-CRP and DAS28-ESR scores *vs* the IFX i.v. group ($P < 0.05$).

At W30, mean CDAI and SDAI scores were significantly lower and mean changes from baseline were significantly improved with IFX s.c. *vs* IFX i.v. ($P < 0.05$; Supplementary Fig. S2, available at *Rheumatology* online). At W54, between-group differences were decreased for both mean CDAI and SDAI scores, although changes from baseline in CDAI and SDAI scores remained significantly greater with IFX s.c. than IFX i.v. (Supplementary Fig. S2, available at *Rheumatology* online).

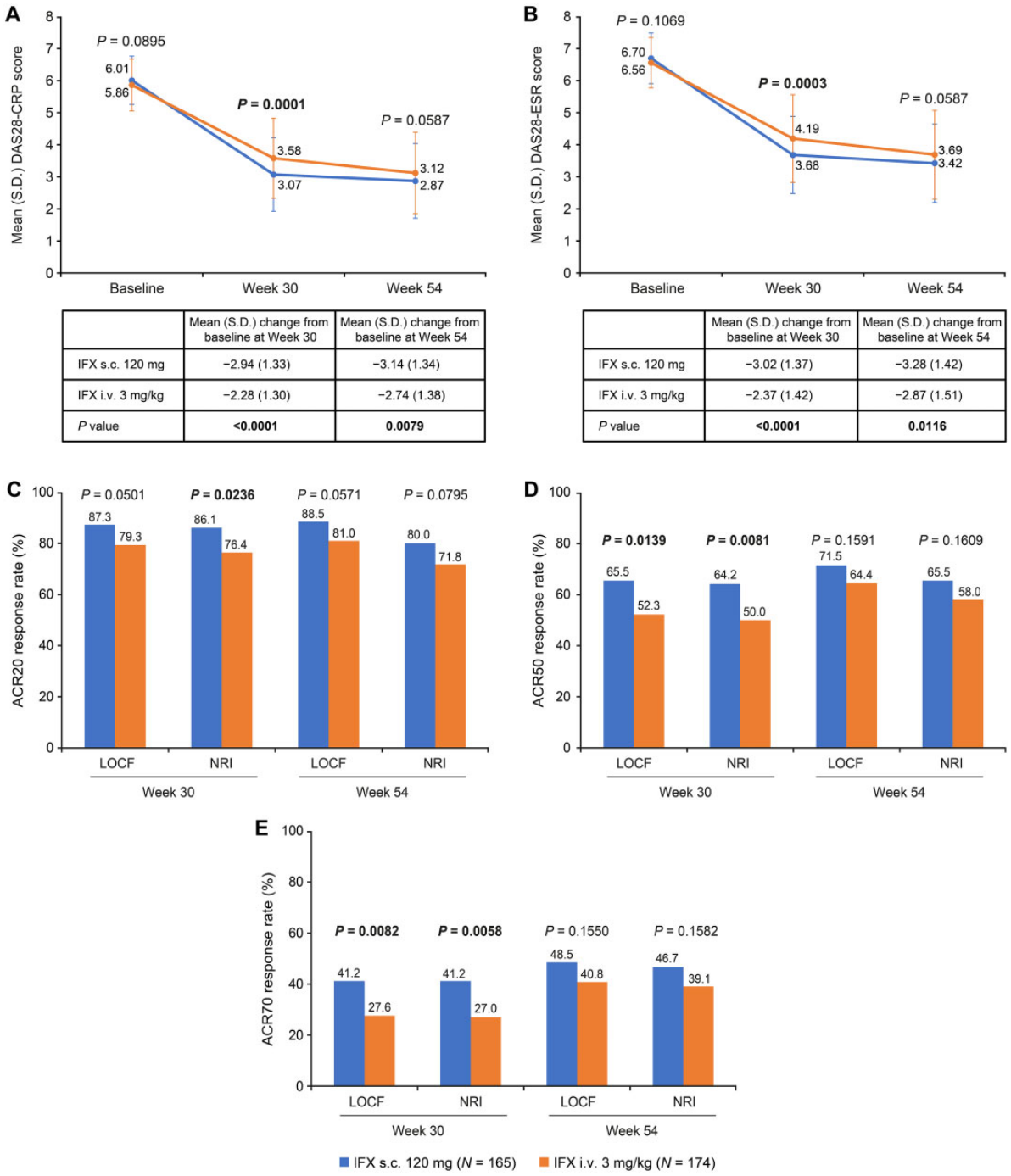
ACR and EULAR responses

At W30, the proportions of patients achieving a 20%, 50% or 70% response per ACR criteria (ACR20, ACR50 or ACR70, respectively) were consistently higher with IFX s.c. *vs* IFX i.v. (with both LOCF and NRI approaches; Fig. 1C–E). These differences were significant for ACR20 with the NRI approach, and for ACR50 and ACR70 with the LOCF and NRI approaches ($P < 0.05$). Between-group differences were reduced at W54 for the ACR20, ACR50 and ACR70 response rates, which were numerically higher in the IFX s.c. than in the IFX i.v. group, but not significantly different ($P > 0.05$).

At W30, the proportions of patients achieving a good EULAR-CRP and EULAR-ESR response were significantly higher with IFX s.c. *vs* IFX i.v. (LOCF/NRI: $P < 0.05$; Supplementary Fig. S3, available at *Rheumatology* online). There was no significant between-group difference in the proportion of patients achieving a moderate EULAR-CRP and EULAR-ESR response (LOCF/NRI: $P > 0.05$), while a significantly lower proportion of patients in the IFX s.c. group compared with the IFX i.v. group achieved no response (LOCF/NRI: $P < 0.05$). At W54, between-group differences were reduced for both EULAR-CRP and EULAR-ESR responses (Supplementary Fig. S3, available at *Rheumatology* online).

Remission and LDA outcomes

At W30, the proportion of patients achieving DAS28-CRP remission was significantly higher in the IFX s.c. *vs* IFX i.v. group (LOCF/NRI: $P < 0.05$; Supplementary Fig. S4, available at *Rheumatology* online), and numerically higher for DAS28-ESR, CDAI remission, SDAI remission, and ACR/EULAR remission (LOCF/NRI: $P > 0.05$). A greater proportion of patients receiving IFX s.c. than IFX i.v. achieved Boolean remission (LOCF: $P < 0.05$; NRI: $P > 0.05$). At W54,



	Mean (S.D.) change from baseline at Week 30	Mean (S.D.) change from baseline at Week 54
IFX s.c. 120 mg	−2.94 (1.33)	−3.14 (1.34)
IFX i.v. 3 mg/kg	−2.28 (1.30)	−2.74 (1.38)
P value	**<0.0001**	**0.0079**

	Mean (S.D.) change from baseline at Week 30	Mean (S.D.) change from baseline at Week 54
IFX s.c. 120 mg	−3.02 (1.37)	−3.28 (1.42)
IFX i.v. 3 mg/kg	−2.37 (1.42)	−2.87 (1.51)
P value	**<0.0001**	**0.0116**

Figure 1. Efficacy outcomes by treatment group (efficacy population). **(A)** Mean (S.D.) score and change from baseline in DAS28-CRP (LOCF approach), **(B)** Mean (S.D.) score and change from baseline in DAS28-ESR (LOCF approach), **(C)** ACR20 response rate (LOCF and NRI approaches), **(D)** ACR50 response rate (LOCF and NRI approaches), and **(E)** ACR70 response rate (LOCF and NRI approaches). ACR20/50/70, 20%/50%/70% response per ACR criteria; CDAI: Clinical Disease Activity Index; DAS28: 28-joint DAS; IFX: infliximab; LOCF: last observation carried forward; NRI: non-responder imputation; SDAI: Simplified Disease Activity Index

a numerical advantage was observed in the IFX s.c. *vs* IFX i.v. group for these outcomes, but between-group differences were not significant ($P > 0.05$). In both groups, the proportion of patients achieving DAS28-CRP/ESR clinical remission was greater at W54 than at W30.

At W30, the proportions of patients achieving LDA, including remission, were significantly higher with IFX s.c. than IFX i.v. for DAS28-CRP, DAS28-ESR, CDAI, and SDAI (LOCF/NRI: $P < 0.05$) (Fig. 2). At W54, between-group differences were reduced, with numerical advantages for the IFX s.c. group observed across outcomes. Between-group differences were not significant, except for DAS28-ESR and SDAI (LOCF: $P < 0.05$), and for CDAI (LOCF/NRI: $P < 0.05$). In both groups, the proportion of patients who achieved LDA determined by DAS28-CRP/ESR was greater at W54 than at W30.

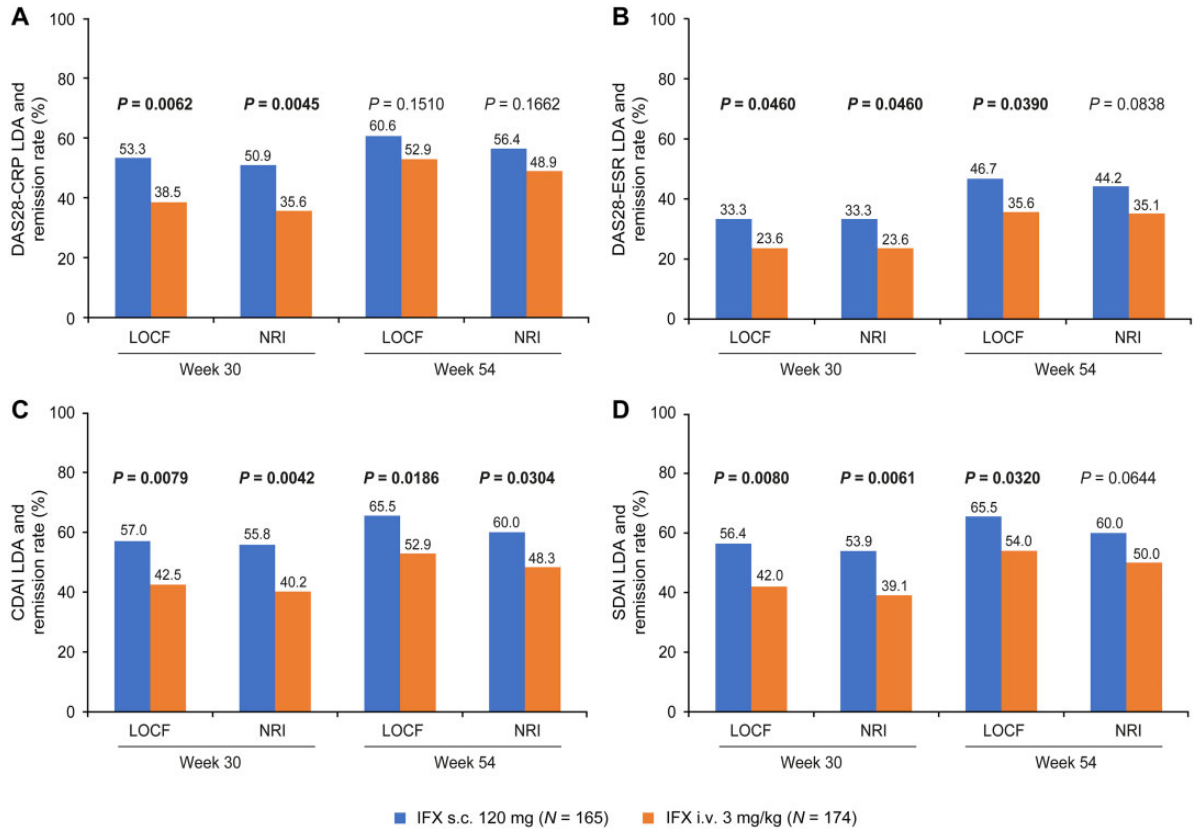


Figure 2. LDA including remission rates by treatment group (efficacy population; LOCF and NRI approaches). **(A)** DAS28-CRP LDA including remission rate, **(B)** DAS28-ESR LDA including remission rate, **(C)** CDAI LDA including remission rate, and **(D)** SDAI LDA including remission rate. CDAI, Clinical Disease Activity Index; DAS28, 28-joint DAS; IFX, infliximab; LDA, low disease activity; LOCF, last observation carried forward; NRI, non-responder imputation; SDAI, Simplified Disease Activity Index

MCID in HAQ score

The proportion of patients achieving an MCID in HAQ score was significantly higher with IFX s.c. than IFX i.v. at W30 (LOCF/NRI: $P < 0.05$; Supplementary Fig. S5, available at *Rheumatology* online), and numerically higher at W54 (LOCF/NRI: $P > 0.05$).

Discussion

In this post-hoc analysis using LOCF and NRI conservative imputation methods, IFX s.c. was associated with significantly greater improvement in most clinical efficacy outcomes compared with IFX i.v. at W30 in patients with active RA. Following the switch to IFX s.c. after W30 in the IFX i.v. group, between-group differences in efficacy parameters appeared to be decreased at W54 compared with W30. Since the efficacy of IFX s.c. was maintained between W30 and W54, these findings may provide evidence suggesting that patients in the IFX i.v. group experienced an improvement in response after switching to IFX s.c.

In this analysis, conservative imputation methods were selected to minimize any bias in determining the effectiveness of IFX s.c. or i.v. Our findings complement those reported in the primary study publication, which did not include statistical analyses but reported greater mean changes from baseline in DAS28-CRP, DAS28-ESR, CDAI and SDAI scores, and numerical advantages for ACR and EULAR response rates, with IFX s.c. *vs* IFX i.v. at W30 [3]. Considerations for handling missing data will become ever more important, as real-world evidence, including from registries, is increasingly recognized in regulatory decision-making [7, 8]. Our findings are also consistent with those of a network meta-regression of individual patient data from an IFX i.v. study (Study 3.1) and the pivotal IFX s.c. study [9].

Recent EULAR recommendations for RA management suggest that therapy should be adjusted if no improvement is observed 3 months after the start of treatment, or if the target has not been reached by 6 months, upon frequent monitoring (every 1–3 months) [4]. In this light, the present findings could be of practical importance in that the proportion of patients who achieved DAS28-CRP clinical remission or LDA was greater at W54 than at W30 (i.e. the nearest observation time point to 6 months in the current study), suggesting that non-responders or partial responders to IFX i.v. therapy after 6 months of treatment could potentially benefit from switching to IFX s.c., not only in terms of pharmacokinetic parameters such as C_{trough} [3], but also in terms of efficacy.

Improvements in efficacy outcomes in the IFX i.v. arm at W54 relative to W30, reflected in the increased between-group similarity, may be explained by the pharmacokinetic profiles described in the primary publication [3]. While serum IFX concentrations were well maintained in both groups throughout the study, the current findings suggest that the more constant exposure over time with IFX s.c. [3] may contribute to improved clinical efficacy outcomes relative to IFX i.v. The potentially improved pharmacokinetic and efficacy profiles with IFX s.c. have led to its citation as a biobetter at an international Delphi consensus meeting [10]. Taken

together with the overall comparability of safety and immunogenicity profiles between IFX s.c. and IFX i.v. [3], these findings suggest that IFX s.c. may offer additional clinical benefits for patients with RA in comparison with IFX i.v.

Our data should reassure patients and health-care providers when considering initiating treatment with or switching to IFX s.c. Potential benefits of s.c. therapeutics include significant time savings for patients, as regular hospital visits for i.v. infusions are not required: indeed, the greater convenience and autonomy offered with s.c. biologics contribute to the preferences of patients with RA for this route of administration [4, 11–13]. In addition, s.c. therapeutics can help to reduce the resource burden of health-care systems, as dedicated infusion services are not required and staff time is not needed for preparing or administering i.v. medications [4]. Furthermore, the availability of both i.v. and s.c. IFX formulations may provide an enhanced choice of biologic treatments of RA [14–19].

In conclusion, this analysis of pivotal study data with NRI and LOCF methods—which are considered conservative imputation methods to avoid bias—confirms that IFX s.c. was associated with greater improvement in most clinical efficacy outcomes compared with IFX i.v. in patients with RA. Switching from IFX i.v. to IFX s.c. was also associated with some improvement in response, providing further evidence for the efficacy of IFX s.c. The positive efficacy outcomes following switching from IFX i.v. to IFX s.c. should provide reassurance for stakeholders, including health-care professionals and patients considering this treatment switch.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Available data and methodological information for this study are included in this article and the accompanying supplementary materials.

Contribution statement

A.C., R.C., C.J.E., J.E.F., F.I., E.K., H.S.-K., S.K., S.Y., D.-H.K. and D.Y. contributed to the interpretation of the data and reviewing of the results. T.K. contributed to the conception and design of the post-hoc analysis and the interpretation of the data. G.P. contributed to the acquisition of data, data analysis, and data interpretation. All authors contributed to manuscript development, had full access to all study data, approved the final manuscript, and agree to be accountable for all aspects of the work.

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