Benefits of anakinra *versus* TNF inhibitors in rheumatoid arthritis and type 2 diabetes: long-term findings from participants furtherly followed-up in the TRACK study, a multicentre, open-label, randomised, controlled trial

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ABSTRACT

Objective. *Interleukin (IL)-1β is considered a shared pathogenic mediator between rheumatoid arthritis (RA) and type 2 diabetes (T2D). In the TRACK study, participants with both diseases were randomised to an IL-1 inhibitor, anakinra, or a TNF inhibitor (TNFi). After 6 months, anakinra induced a such of improvement on metabolic and inflammatory parameters, leading to a premature stoppage of the study. Thus, we aimed to assess how long IL-1 inhibition benefits lasted.*

Methods. *Since the TRACK was prematurely discontinued for "early benefit", we furtherly followed-up the enrolled participants to assess how long persisted the improvement of glycated haemoglobin (HbA1c%) and of RA disease activity.*

Results. *After a mean follow-up of 18 months (15 participants in anakinra-group and 14 in TNFi-group), RA clinical response was retained in both groups (DAS28: 2.59±1.01 vs. 2.88±0.91; p=0.109). Concomitant glucocorticoids were reduced in both groups (2.01±0.71 vs. 3.01±0.87 mg/die; p=0.124), but a larger percentage of anakinra-treated participants discontinued such drugs (53.3% vs. 28.6%; p=0.004). There was no difference between anakinra and TNFi for HbA1c% (6.60±0.52 vs. 6.79±0.43; p=0.291), but a reduction of anti-diabetic drugs was observed in anakinra-treated participants (53.3% vs. 7.1%; p=0.008) whereas an increase of anti-diabetic therapies was needed in TNFi-treated ones. Significant correlations were also observed among HbA1c% with DAS28 and with C-reactive protein. Analysing the safety profile, only minor side effects were recorded.*

Conclusion. *Data deriving from the long-term extension of participants with RA and T2D, enrolled in the TRACK study, could suggest that the benefits of IL-1 inhibition on metabolic and inflammatory parameters could last longer than first 6 months of follow-up, but further studies are needed to confirm these findings.*

Introduction

Interleukin (IL)-1β is considered a shared pathogenic mediator between rheumatoid arthritis (RA) and type 2 diabetes (T2D) (1, 2). In this context, the TRACK [Treatment of Rheumatoid Arthritis and Comorbidities with Kineret (anakinra)] study suggested that IL-1 inhibition by anakinra, a human interleukin-1-receptor antagonist, improved both metabolic and inflammatory parameters in patients with RA and T2D (3). After 6 months, anakinra induced a significant improvement of metabolic alterations whereas TNF inhibitors (TNFis) did not (crude difference 0.93 of glycated haemoglobin%, HbA1c%, between groups). Simultaneously, the majority of anakinra-treated participants achieved RA remission or minimal disease activity. Due to larger benefits observed in anakinra group, the TRACK study was prematurely stopped for "early benefit" (3). Based on the "real-life" design, we furtherly followed-up these participants and descriptively assessed how long lasted the improvement of HbA1c% and of RA disease activity, including the rate of reduction and discontinuation of both anti-diabetic drugs and glucocorticoids (GCs). We also correlated metabolic and inflammatory parameters to assess possible relationships.

Participants and methods

The TRACK study was a multicentre, randomised, open-label, prospective, controlled, parallel-group study to investigate whether IL-1 inhibition with anakinra could induce improvement in both metabolic and inflammatory parameters in participants with RA and T2D when compared with TNFis [EudraCT: 2012-005370-62; ClinicalTrial.gov: NCT02236481]. This study was designed as a non-profit study, according to Italian law "*Decreto Ministero della Salute 17 Dicembre 2004*", to support independent research in Italy. More details about study design, inclusion criteria, randomisation, interventions, and endpoints are available elsewhere (3). This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) guideline (3). Considering the original scheduled follow-up of 24 months, the present evaluation aimed to descriptively assess how long persisted the improvement of HbA1c%

Table I. Clinical characteristics of randomised participants in the TRACK clinical trial and followed up after the premature discontinuation of the study.

	Anakinra	TNFi	*p*-value
Baseline characteristics			
Number of participants	22	17	–
Age, mean ± SD	62.86 ± 9.70	62.53 ± 10.60	–
Female gender, n (%)	17 (77.2%)	12 (70.6%)	–
DAS28, mean ± SD	5.43 ± 1.18	5.70 ± 0.80	–
GCs, n (%)	13 (59.1%)	13 (76.5%)	–
GCs, mean ± SD	5.83 ± 1.08	5.09 ± 1.48	–
HbA1c%, mean ± SD	7.73 ± 0.67	7.83 ± 0.76	–
Anti-diabetic drugs, n (%)	22 (100.0%)	17 (100.0%)	–
Oral anti-diabetic drugs, n (%)	18 (81.8%)	11 (64.7%)	–
Insulin, n (%)	6 (27.3%)	4 (23.5%)	–
6-month follow-up			
Number of participants	17	15	–
DAS28, mean ± SD	2.70 ± 1.16	3.58 ± 1.45	0.081
Good EULAR response, n (%)	16 (94.1%)	9 (60.0%)	**0.030**
Remission, n (%)	9 (52.9%)	4 (26.7%)	0.176
Discontinuation of GCs, n (%)	8 (47.1%)	4 (26.7%)	0.465
GCs, mean ± SD	2.77 ± 0.98	3.91 ± 1.91	0.318
HbA1c%, mean ± SD	6.70 ± 0.67	7.64 ± 0.65	**<0.001**
Anti-diabetic drugs, n (%)	13 (76.5%)	15 (100%)	0.104
Oral anti-diabetic drugs, n (%)	10 (58.8%)	13 (86.7%)	0.465
Insulin, n (%)	3 (17.6%)	2 (13.3%)	0.737
Reduction of anti-diabetic drugs*, n (%)	8 (47.0%)	1 (6.7%)	**0.018**
Last follow-up			
Number of participants	15	14	–
Median last follow-up, months	18 (12-24)	18 (12-24)	0.999
DAS28, mean ± SD	2.59 ± 1.01	2.88 ± 0.91	0.109
Good EULAR response, n (%)	15 (100.0%)	11 (78.5%)	0.062
Remission, n (%)	10 (66.7%)	5 (35.7%)	0.518
Discontinuation of GCs, n (%)	8 (53.3%)	4 (28.6%)	**0.004**
GCs, mean ± SD	2.01 ± 0.71	3.01 ± 0.87	0.124
HbA1c%, mean ± SD	6.60 ± 0.52	6.79** ± 0.43	0.291
Anti-diabetic drugs, n (%)	11 (73.3%)	14 (100%)	0.329
Oral anti-diabetic drugs, n (%)	9 (60.0%)	12 (85.7%)	0.215
Insulin, n (%)	2 (13.3%)	2 (14.2%)	0.999
Reduction of anti-diabetic drugs, n (%)	8 (53.3%)	1 (7.1%)	**0.008**
Minor side effects, n (%)	8 (53.3%)	4 (28.6%)	0.234
Urticarial lesions in injection site, n (%)	4 (26.7%)	1 (7.1%)	0.170

*The reduction of anti-diabetic drugs was defined as the reduction of administered dosages, change from combination therapy to monotherapy, or discontinuation of anti-diabetic drugs.
**The reduction of HbA1c% was achieved after the increase of anti-diabetic drugs in TNFi-treated patients.

and of RA disease activity, since the TRACK was prematurely discontinued for "early benefit". Disease activity score in 28 joints (DAS28) was used to assess the disease activity (3). The analysis has been performed only in participants who were not lost to the follow-up since the descriptive purposes of this evaluation. The rate of reduction and discontinuation of both anti-diabetic drugs and GCs was also assessed. The reduction of anti-diabetic drugs was defined as the significant reduction of administered dosages, change from combination therapy to monotherapy, or discontinuation of anti-diabetic drugs. Given the open label-design, the reduction of concomitant therapies was left to the physician in charge of the participant.

The study was approved by the local ethics committee (*Comitato Etico ASL1 Avezzano-Sulmona-L'Aquila*, L'Aquila, Italy; protocol no. 0020902/13), and the study was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consent was obtained from all participants before any study-related procedure.

Results

Descriptive statistics of enrolled participants are reported in Table I, more details are available elsewhere (3). Considering the last available observation (mean follow-up 18 months) of enrolled participants, we performed this evaluation. The participants who were not considered were those lost to follow-up after the first 6 months. Assessing RA disease activity, the clinical response was retained during the whole follow-up in both groups, as per maintenance of reduced levels of DAS28. The rate of good EULAR response as well as of remission persisted during the follow-up and did not differ in both groups. Furthermore, a larger percentage of anakinra-treated participants discontinued the concomitant GCs therapy (p=0.004). In assessed participants, a persistence of reduced HbA1c% levels were observed in anakinra group (baseline: 7.73%±0.67; 6 months: 6.70%±0.67; last follow-up: 6.60%±0.52), leading to a significant reduction of anti-diabetic therapies (p=0.008). One participant reduced insulin dosages, 1 switched from insulin to an oral anti-diabetic therapy, 2 changed their combination therapy with 2 anti-diabetic drugs to a monotherapy, and 4 out of 15 (26.7%) discontinued their oral anti-diabetic drugs. On the contrary, an increase of anti-diabetic therapies was needed in TNFi-treated participants to reduce HbA1c% levels, both insulin dosages and oral anti-diabetic drugs. Considering the efficacy on joint involvement, physicians preferred to continue TNFi and to increase anti-diabetic therapies on those participants, despite the rate of HbA1c% reduction in anakinra group.

We also observed significant correlations bteween HbA1c% with DAS28 (R=0.54, p=0.0014) and with C-reactive protein (CRP) (R=0.37, p=0.037), after 6 months. Similar results were observed correlating fasting plasma glucose (FPG) with same parameters (Fig. 1). In fact, FPG correlates with DAS28 (R=0.61, p=0.0002 and with CRP (R=0.59, p=0.0002).

Analysing the safety profile, as observed in first 6 months of the study (3), only minor side effects were recorded during the whole follow-up with no difference between groups, except for more frequent self-limited urticarial lesions at the injection site in anakinra group.

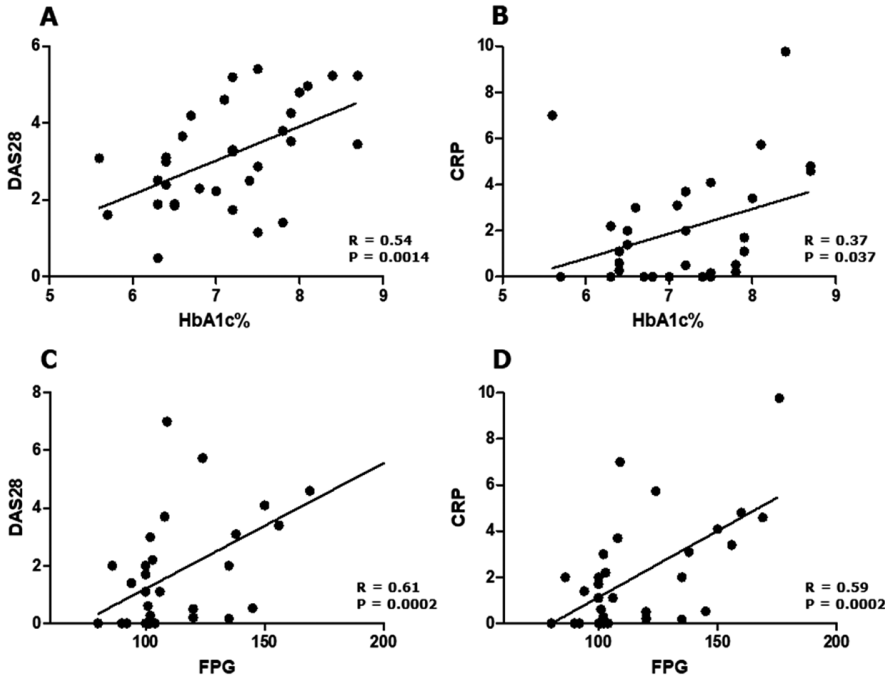

Fig. 1. Correlation among inflammatory and metabolic parameters after 6 months of follow-up.
A: HbA1c% correlates with DAS28 (R=0.54, *p*=0.0014).
B: HbA1c% correlates with CRP (R=0.37, *p*=0.037).
C: FPG correlates with DAS28 (R=0.61, *p*=0.0002).
D: FPG correlates with CRP (R=0.59, *p*=0.0002).

Discussion

Following IL-1 inhibition in the TRACK study, the benefits on metabolic and inflammatory parameters lasted longer than first 6 months of follow-up on participants with RA and T2D. In anakinra-treated participants, the reduction of HbA1c% levels persisted during the follow-up and was associated with a significant reduction of anti-diabetic therapies. On the contrary, an increase of such therapies was needed in TNFi-treated participants to reduce HbA1c% levels. Current therapies for T2D improve glycaemia, but none has shown disease-modifying effects so far. Conversely, IL-1 inhibition could not only palliate glycaemia, but also decrease the progressive decline in insulin secretion, interfering with apoptosis of pancreatic beta-cells, improving their secretory function, and ameliorating the peripheral insulin resistance (1, 4). Considering our more pronounced decrease of HbA1c% than previous study on T2D (5), we could hypothesise that the pro-inflammatory mechanisms of T2D are exaggerated by RA and anakinra could counteract a pathogenic vicious circle perpetuated through glucose derangement, inflammation, and IL-1β (1-4). In fact, the stimulation with high levels of glucose induced a significant production of IL-1β in monocytes obtained from patients with RA and T2D than those from RA or T2D (6). Furthermore, the correlations among HbA1c% and FPG with RA inflammatory process could also reinforce the idea of a possible pathogenic link between these diseases. Moreover, the maintenance of clinical remission could improve the glucose derangement and reduce the occurrence of T2D in RA (7). The persistent clinical response of anakinra-treated participants appeared to be in conflict with previous results on RA (8). TRACK participants showed a relatively short disease duration and were classified according to 2010 ACR/EULAR criteria (3). Unlike those meeting the 1987 criteria, these patients may have a less severe disease course, developing a less severe radiological joint damage, and achieving more often a clinical remission, also a synthetic DMARD-free remission (9). The maintenance of remission is also associated with the discontinuation of concomitant GCs therapy, as observed in anakinra group, contributing to the reduction of their metabolic side effects (10).

Patients with RA and T2D have a high risk of cardiovascular disease (11), thus the simultaneous improvement of both glycaemic abnormalities and inflammatory activity in anakinra-treated participants could counteract the synergy between "traditional" cardiovascular risk factors and inflammation in enhancing the atherosclerotic burden (11, 12). Thus, new therapeutic strategies could be provided better stratifying these patients with RA according to their clinical picture and associated comorbidities in improving their long-term outcomes (2, 13).

Analysing the safety profile, as observed in first 6 months of the study (3), only minor side effects were recorded during the whole follow-up.

The present evaluation is burdened by different limitations and the results should be cautiously generalised and interpreted. These limitations are mainly related to the open-label design and the relatively low number of assessed participants, because of the early stoppage of the study. Considering the small number of enrolled participants, our results could be biased since these could have a good prognosis and not representative of whole RA population. In addition, further confirmatory studies are needed to fully elucidate this issue of long-term maintenance of metabolic benefits following IL-1 inhibition. Conflicting results are available on this topic; no consistent long-term benefits on HbA1c or FPG were observed following canakinumab whereas an improvement of glycaemic parameters was still present 39 weeks after discontinuation of anakinra in T2D patients (14, 15). The different mechanism of action of these drugs, either a human monoclonal antibody targeting IL-1β or an interleukin-1 receptor antagonist blocking both IL-1α and IL-1β, could possibly explain this discrepancy and could provide the rationale of designing further studies with a long follow-up and adequately powered to entirely elucidate this topic.

In conclusion, data deriving from the long-term extension of participants with RA and T2D, enrolled in the TRACK study, could suggest that the

benefits of IL-1 inhibition on metabolic and inflammatory parameters lasted longer than the first 6 months of follow-up. Considering the pronounced decrease of HbA1c% during the follow-up and the correlations between metabolic and inflammatory parameters, it could be possible to hypothesise that the pro-inflammatory mechanisms of T2D could be exaggerated by RA and anakinra could counteract a pathogenic vicious circle perpetuated through glucose derangement, inflammation, and IL-1β. Thus, the presence of T2D could identify a subset of RA likely benefitting of IL-1 inhibition, although further confirmatory studies are needed with a longer follow-up and adequately powered to entirely elucidate this topic stratifying the patients according to their clinical picture and associated comorbidities.

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References

1. DONATH MY, DINARELLO CA, MANDRUP-POULSEN T: Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol* 2019; 19: 734-46.
2. GIACOMELLI R, RUSCITTI P, ALVARO S *et al*.: IL-1β at the crossroad between rheumatoid arthritis and type 2 diabetes: may we kill two birds with one stone? *Expert Rev Clin Immunol* 2016; 12: 849-55.
3. RUSCITTI P, MASEDU F, ALVARO S *et al*.: Anti-interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (TRACK): A multicentre, open-label, randomised controlled trial. *PLoS Med* 2019; 16: e1002901.
4. RUSCITTI P, URSINI F, CIPRIANI P *et al*.: IL-1 inhibition improves insulin resistance and adipokines in rheumatoid arthritis patients with comorbid type 2 diabetes: An observational study. *Medicine* (Baltimore) 2019; 98: e14587.
5. LARSEN CM, FAULENBACH M, VAAG A *et al*.: Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N Engl J Med* 2007; 356: 1517-26.
6. RUSCITTI P, CIPRIANI P, DI BENEDETTO P *et al*.: Monocytes from patients with rheumatoid arthritis and type 2 diabetes mellitus display an increased production of interleukin (IL)-1β via the nucleotide-binding domain and leucine-rich repeat containing family pyrin 3(NLRP3)-inflammasome activation: a possible implication for therapeutic decision in these patients. *Clin Exp Immunol* 2015; 182: 35-44.
7. RUSCITTI P, URSINI F, CIPRIANI P *et al*.: Poor clinical response in rheumatoid arthritis is the main risk factor for diabetes development in the short-term: A 1-year, single-centre, longitudinal study. *PLoS One* 2017; 12: e0181203.
8. NUKI G, BRESNIHAN B, BEAR MB *et al*.: Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 2838-46.
9. BYKERK VP, JAMAL S, BOIRE G *et al*.: The Canadian Early Arthritis Cohort (CATCH): patients with new-onset synovitis meeting the 2010 ACR/EULAR classification criteria but not the 1987 ACR classification criteria present with less severe disease activity. *J Rheumatol* 2012; 39: 2071-80.
10. BERARDICURTI O, RUSCITTI P, PAVLYCH V *et al*.: Glucocorticoids in rheumatoid arthritis: the silent companion in the therapeutic strategy. *Expert Rev Clin Pharmacol* 2020; 13: 593-604.
11. NURMOHAMED MT, HESLINGA M, KITAS GD: Cardiovascular comorbidity in rheumatic diseases. *Nat Rev Rheumatol* 2015; 11: 693-704.
12. ROMANO S, SALUSTRI E, RUSCITTI P, CARUBBI F, PENCO M, GIACOMELLI R: Cardiovascular and metabolic comorbidities in rheumatoid arthritis. *Curr Rheumatol Rep* 2018; 20: 81.
13. SILVAGNI E, DI BATTISTA M, BONIFACIO AF, ZUCCHI D, GOVERNATO G, SCIRÈ CA: One year in review 2019: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 519-34.
14. LARSEN CM, FAULENBACH M, VAAG A, EHSES JA, DONATH MY, MANDRUP-POULSEN T: Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care 2009*; 32: 1663-8.
15. EVERETT BM, DONATH MY, PRADHAN AD *et al*.: Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018; 71: 2392-401.