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LETTER TO THE EDITOR

Successful response to tralokinumab in patients unresponsive, intolerant or with contraindications to dupilumab and JAK inhibitors: A case series

Dear Editor,

The recent approval of novel targeted therapies that included two biologics (dupilumab and tralokinumab) and three small molecules consisting of Janus kinase (JAK) inhibitors (abrocitinib, baricitinib and upadacitinib) has profoundly changed the long-term management of moderate-to-severe atopic dermatitis (AD).[1,2] Though an optimal control may be obtained, a proportion of patients are unresponsive, intolerant or have contraindications to these therapeutic agents.

Tralokinumab has demonstrated a favourable efficacy and safety profile in the treatment of moderate-to-severe AD in both clinical trials and real-life experiences.[3–5] However, there is scarce evidence regarding tralokinumab response in difficult-to-treat patients presenting a relevant therapeutic unmet need, being unresponsive, intolerant or presenting contraindications to any available targeted therapy (namely dupilumab and JAK inhibitors).[6] We identified 17 difficult-to-treat patients (11 females [64.7%], mean age: 58.5 ± 19.0 years), who had previously failed either dupilumab (17/17, 100%) or upadacitinib (9/17, 52.9%), while the use of JAK inhibitors was not recommended in 8/17 (47.1%) patients due to comorbidities (ischemic heart disease in 2 cases and 1 case for each of the following comorbid conditions: history of thromboembolism, HBcAb positivity, recurrent herpes zoster, recent history of melanoma, concomitant cardiovascular risk factors and metabolic syndrome). This high-need patient subcohort ($n = 17$ patients) showed no significant differences in terms of disease severity assessed at the time of study enrolment, compared with patients treated with tralokinumab as first line immune-targeted therapy (named naive patients, $n = 126$). Mean Eczema Area Severity Index (EASI) score [23.1 ± 11.8 vs. 22.5 ± 8.3, $p = 0.798$], mean Itch- and Sleep-numerical rating scale (NRS) values (Itch-NRS: 7.7 ± 2.7 vs. 7.3 ± 2.1, $p = 0.425$; Sleep-NRS: 6.1 ± 3.4 vs. 4.6 ± 3.5, $p = 0.099$) and mean dermatology life quality index (DLQI) score (11.6 ± 7.5 vs. 11.4 ± 6.4, $p = 0.925$) resulted not significantly different between difficult-to-treat and naive patient subcohorts. Nor clinic-demographic discrepancies in terms of age at disease onset ($p = 0.129$), IgE serum levels ($p = 0.525$) or eosinophil cell count ($p = 0.229$), AD pattern ($p = 0.303$) or phenotype ($p = 0.404$) were detected. A significant higher age at treatment initiation was found among difficult-to-treat than naive patients (57.9 ± 19.5 vs. 41.5 ± 18.6, $p = 0.0009$).

Significant improvements from baseline were detected among difficult-to-treat cohort for both patient-oriented disease severity scores and physician-based assessment scores as early as Week 4 and were sustained throughout the 32 weeks of observation (Table 1). At Week 16, EASI 50 and EASI 75 responses were achieved by 65% and 35.3%, respectively, with an increasing percentage of patients achieving EASI 50, EASI 75 and EASI 90 responses (80%, 50% and 20%, respectively).

These findings are consistent with data reported in the ECZTRA 3 clinical trial, related to the clinical response at Week 16 as well as to the progressive and sustained improvement in disease activity observed throughout the 32 weeks of observation.[3] Four of 17 (23.5%) patients experienced an adverse event (AE), including telogen effluvium (1 case), headache (1 case), injection site reaction (1 case) and spontaneous intracranial haemorrhage that was considered as unrelated to tralokinumab exposure (1 case). In total, 5/17 patients (29.4%) discontinued treatment: 3 due to ineffectiveness (one at Week 4 and 2 at Week 16), and 2 due to the occurrence of AEs. Noteworthy, the three patients (2 female; mean age: 63 years) who discontinued treatment due to ineffectiveness exhibited a higher disease burden at baseline compared to the rest of the study cohort ($n = 14$), with a mean EASI score of 29 compared to 20.7, respectively.

In conclusion, tralokinumab obtained a favourable clinical response as second or third line of treatment in the management of difficult-to-treat patients who presented a highly relevant therapeutic unmet need, resulting unresponsive, intolerant or had contraindications to multiple lines of systemic therapies, including dupilumab and JAK inhibitors.

†MEDaCoTRA Study Group members presented in Appendix A.

TABLE 1 Mean values of EASI, DLQI, ITCH-NRS and SLEEP-NRS and % of patients reaching IGA0/1 and EASI 50, 75 and 90 at each time point.

	Baseline	Week 4	Week 16	Week 32
Patients achieving EASI 50 response, % (*n*)	–	65 (11/17)	80 (8/10)	75 (3/4)
Patients achieving EASI 75 response, % (*n*)	–	35.3 (6/17)	50 (5/10)	50 (2/4)
Patients achieving EASI 90 response, % (*n*)	–	5.8 (1/17)	20 (2/10)	50 (2/4)
Patients achieving ≥4-point improvement in Itch NRS, % (*n*)	–	35.3 (6/17)	40 (4/10)	50 (2/4)
Mean EASI score ± SD*	23.1 ± 11.8	9.8 ± 9.6	7.2 ± 10.0	4.8 ± 4.9
Mean Itch-NRS ± SD*	7.7 ± 2.7	5.0 ± 3.3	3.3 ± 3.4	3.0 ± 2.1
Mean Sleep-NRS ± SD*	6.1 ± 3.4	2.8 ± 2.4	3.1 ± 3.1	4.0 ± 3.2
Mean DLQI score ± SD*	11.6 ± 7.5	7.25 ± 3.9	4.5 ± 3.2	3.0 ± 3.2

*$p < 0.001$ for each time point versus baseline.

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Activity Severity Index; NRS, Numeric Rating Scale; SD, standard deviation.

FUNDING INFORMATION

No funding sources supported this study.

CONFLICT OF INTEREST STATEMENT

Outside of the submitted work, authors declare the following conflicts of interest: ***Anna Balato*** has served as speaker and/or consultant for Abbvie, Amgen, Boehringer Ingelheim, Eli-Lilly, Novartis and UCB. ***Luca Bianchi*** declares to have acted as a speaker and consultant for AbbVie, Novartis, Janssen-Cilag, Pfizer, UCB and LeoPharma, outside the submitted work. ***Andrea Chiricozzi*** has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Boehringer-Ingelheim, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme. ***Curdin Conrad*** has been scientific adviser and/or clinical study investigator for AbbVie, Actelion, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli-Lilly, Incyte, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Samsung, Sanofi and UCB. ***Silvia Ferrucci*** has been principal investigator in clinical trials for ABBVIE, Almirall, Galderma, Leo Pharma, Sanofi, Amgen, Novartis and Bayer and received honoraria for lectures for Novartis and Menarini. ***Marco Galluzzo*** declared to have acted as speakers and/or consultants for AbbVie, Almirall, Eli-Lilly, Janssen-Cilag, LeoPharma, Novartis and Sanofi, outside the submitted work. ***Giampiero Girolomoni*** has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer- Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Samsung and Sanofi. ***Niccolò Gori*** served as advisory board member and received honoraria for lectures for AbbVie, Sanofi and Leo-Pharma. ***Angelo Valerio Marzano*** reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi and UCB. ***Michela Ortoncelli*** has served as advisory board member and/or consultant and has received fees and speaker's honoraria or has participated for clinical studies for AbbVie, Leo Pharma and Sanofi Genzyme. ***Ketty Peris*** has served on advisory board and received honoraria for lectures and/or research grants for Abbvie, Almirall,Lilly, Galderma, Leo Pharma, Pierre Fabre, Novartis, Sanofi, Sun Pharma and Janssen. ***Simone Ribero*** has served as advisory board member and/or consultant and has received fees and speaker's honoraria or has participated for clinical studies for AbbVie, Almirall, Leo Pharma, Elli Lilly, Novartis, Pfizer and Sanofi Genzyme. The other authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

Enquiries related to the data generated or analysed during this study can be directed to the corresponding author.

ETHICS STATEMENT

The patients included in this study have given written informed consent to publication of their case details.

ETHICAL APPROVAL

Approval of this study was obtained by the Local Ethics Committee—Comitato Etico Territoriale (CET) Lazio Area 3, Prot. ID: 5909.

Niccolò Gori[1,2]
Elena Ippoliti[1,2]
Silvia Mariel Ferrucci[3]
Anna Balato[4]
Michela Ortoncelli[5]
Martina Maurelli[6]
Marco Galluzzo[7,8]
Monica Munera Campos[9]
Teofila Seremet[10]
Lucia Di Nardo[1,2]
Flaminia Antonelli[1,2]
Giulia Coscarella[1,2]
Curdin Conrad[10]
Jose Manuel Carrascosa[9]
Luca Bianchi[7,8]
Giuseppe Argenziano[4]
Simone Ribero[5]
Giampiero Girolomoni[6]
Angelo Valerio Marzano[3,11]
Andrea Chiricozzi[1,2]

Ketty Peris[1,2]
MEDaCoTRA Study Group†

[1]*Dermatologia, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy*
[2]*Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[3]*Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[4]*Unit of Dermatology—University of Campania Luigi Vanvitelli, Naples*
[5]*Section of Dermatology, Department of Medical Sciences, University of Turin, Turin, Italy*
[6]*Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy*
[7]*Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy*
[8]*Dermatology Unit, Fondazione Policlinico "Tor Vergata", Rome, Italy*
[9]*Department of Dermatology, Germans Trias i Pujol University Hospital (HUGTP), Autonomous University of Barcelona (UAB), Badalona, Spain*
[10]*Department of Dermatology, Lausanne University Hospital CHUV and University of Lausanne, Lausanne, Switzerland*
[11]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy*

Correspondence
Andrea Chiricozzi, Dermatologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy.
Email: chiricozziandrea@gmail.com

Niccolò Gori and Elena Ippoliti contributed equally to this work and shared the first authorship.

ORCID

Niccolò Gori https://orcid.org/0000-0003-1987-0623
Martina Maurelli https://orcid.org/0000-0001-7492-8010
Marco Galluzzo https://orcid.org/0000-0002-3424-5175
Monica Munera Campos https://orcid.org/0000-0002-2227-2993
Lucia Di Nardo https://orcid.org/0000-0002-2087-7526
Curdin Conrad https://orcid.org/0000-0002-2547-3440
Jose Manuel Carrascosa https://orcid.org/0000-0003-4266-0771
Giuseppe Argenziano https://orcid.org/0000-0003-1413-8214
Simone Ribero https://orcid.org/0000-0002-0098-1406
Giampiero Girolomoni https://orcid.org/0000-0001-8548-0493
Angelo Valerio Marzano https://orcid.org/0000-0002-8160-4169
Andrea Chiricozzi https://orcid.org/0000-0002-6739-0387
Ketty Peris https://orcid.org/0000-0003-1957-6600

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APPENDIX A

MEDaCoTRA Study Group: Eugenia Veronica Di Brizzi[4] MD, Nicole Macagno[5], Luca Mastorino[5] MD, Claudia Paganini[7] MD, Marina Talamonti[8] MD.