Tremfya®
(guselkumab)

FÜR MICH EIN TRIUMPH.#

NON-STOP
im Leben.

PSO* + PSA*

TREMFYA®–
der erste IL-23-Hemmer, der beides kann!

HEISSE NEWS
aus der GUIDE-Studie.
Hier mehr erfahren ...

* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0,0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

TREMFYA® 100 mg Injektionslösung in einer Fertigspritze/ in einem Fertigpen. Wirkstoff: Guselkumab. **Zusammensetz.:** Fertigspritze/Fertigpen enth. 100 mg Guselkumab. Sonst. Bestandt.: Histidin, Histidinmonohydrochlorid-Monohydrat, Polysorbat 80, Sucrose, Wasser f. Injektionszw.. **Anw.geb.:** Für d. Bhdlg. erw. Pat. m. mittelschwerer bis schwerer Plaque-Psoriasis indiziert, d. für e. syst. Therapie in Frage kommen. Als Monotherapie od. in Komb. m. Methotrexat für d. Bhdlg. erw. Pat. m. Psoriasis-Arthritis indiziert, d. auf e. vorherige nicht-biolog. krankheitsmodifiz. antirheumat. (DMARD)-Therapie unzureich. angesprochen od. diese nicht vertragen haben. **Gegenanz.:** Schwerwieg. Überempfindl. gg. Guselkumab od. e. d. sonst. Bestandt., klin. relev. aktive Infektionen (einschl. aktive Tuberkulose), Schwangersch., Stillzeit. **Bes. Warnhinw. u. Vorsichtsmaßn.:** Um d. Rückverfolgbark. b. biolog. Arzneim. zu verbessern, sollten Name u. Ch.-Bez. d. verabreich. Prod. deutl. protokoll. werden. Vors. b. Infektionen, Tuberkulose, Impfungen (vor Anw. v. Lebendimpfst. muss d. Bhdlg. m. Tremfya nach d. letzt. Gabe f. mind. 12 Wo. ausgesetzt werden). B. Erhöh. v. Leberenzymwerten (ALT/AST) u. Verdacht auf arzneimittelinduz. Leberschädig. sollte d. Bhdlg. vorüberg. unterbr. werden. B. schwerwieg. Überempfindl.reakt. sollte d. Anw. v. Tremfya unverzügl. abgebrochen u. e. geeign. Bhdlg. eingel. werden. Frauen im gebärfäh. Alter sollen währ. u. f. mind. 12 Wo. nach d. Bhdlg. e. zuverläss. Verhütgs.meth. anw.. Arzneim. f. Kdr. unzugängl. aufbewahren. **Nebenwirk.:** *Sehr häufig* (≥ 1/10), *Häufig* (≥ 1/100 bis < 1/10), *Gelegentlich* (≥ 1/1.000 bis < 1/100). *Sehr häufig:* Atemwegsinfekt.. *Häufig:* Kopfschm., Diarrhoe, Arthralgie, Reakt. a. d. Injektionsst., Transamin. erhöht. *Gelegentlich:* Herpes-simpl-Infekt., Tinea-Infekt., Gastroenteritis, Überempfindl.reakt., Anaphylaxie, Urtikaria, Hautausschlag, Neutrophilenzahl erniedr.. Verschreibungspflichtig. **Pharmazeut. Unternehmer:** JANSSEN-CILAG International NV, Turnhoutseweg 30, B-2340 Beerse, Belgien. **Örtl. Vertreter für Deutschland:** Janssen-Cilag GmbH, Johnson & Johnson Platz 1, D-41470 Neuss. **Stand d. Inform.:** 12/2020.

CP-274718

Janssen-Cilag GmbH
www.tremfya-pso.de

janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Clinical Letter

Diagnostic next generation sequencing in neonatal erythroderma

DOI: 10.1111/ddg.14298

Dear Editors,

The list of differential diagnoses of neonatal erythroderma (NE) is long. Ichthyoses, immunodeficiencies and infections are the most frequent underlying causes while metabolic disorders, drugs and more rare causes such as atopic dermatitis, psoriasis and seborrheic dermatitis are the less frequent [1, 2]. Neonatal erythroderma is often accompanied by a collodion membrane. A correct diagnostic approach to neonatal erythroderma is difficult based on the clinical presentation alone. To our knowledge, this is the first report on the application of next generation sequencing (NGS) in a cohort of patients with NE as main inclusion criterium. This study revealed a variety of genetic diagnoses. Next generation sequencing was proven to be particularly valuable for detecting life-threatening disorders that are difficult to clinically recognize in the early stages in NE patients without a collodion.

To obtain a definite genetic diagnosis in 23 patients, NGS was performed prospectively (September 1, 2014–January 1, 2018) in 15 patients at birth and retrospectively in eight patients born before September 1, 2014 in which a definite diagnosis was not present yet. The NGS panel was regularly updated during the study. The last version of the NGS panel as present on January 1, 2018 was run on patients without a genetic diagnosis earlier in the study. Non-genetic diagnoses such as infections or drug-use were less plausible based on history, laboratory results and clinical characteristics. Informed consent was obtained from parents of the patients along with approval of the medical ethics committee.

A targeted NGS panel of 60 genes associated with neonatal erythroderma and collodion membrane was used (see Table S1 in the online supplement), based on extensive literature search. The gene panel comprised uniquely mapped coding regions of 60 genes from the built genome GRCh37/hg19 (www.ncbi.nlm.nih.gov/assembly/2758) as well as 50 bp flanks into intronic regions. The DNA was enriched using the SureSelect XT Target or Human All Exon v5 kit (Agilent Technologies B. V. Netherlands) and sequenced using the HiSeq2500 system on rapid run mode (Illumina, Netherlands) at a mean target depth of 100x. The reads were aligned to hg19 using BWA (BWA-MEM v0.7.5a); variants were called using the GATK haplotype caller (v2.7-2). The correlation between the diagnosis and clinical presentation (erythroderma or collodion) was calculated using the odds ratio and chi-squared tests.

A genetic diagnosis was found in 70 % of the cases (16/23) (Table 1); 60 % in the prospective cohorts (9/15) and 88 % (7/8) in the retrospective cohorts, respectively. A collodion membrane was present in 14/23 patients (61 %) of which 12 (86 %) had an underlying type of ichthyosis. Mutations linked to ichthyoses were found in the genes: *TGM 1* (4/14), *ALOX12B* (3/14), *PNPLA1*, *ABCA12*, *ALOXE3*, *KRT10* and *ALDH3A2* [1/14 each]. In two collodion patients, no definite genetic diagnosis could be made; variants of unknown significance (VUS) were found in *BTD* and *ALOX12B*, which were unlikely to have contributed to the clinical presentation. In patients without a collodion membrane, an underlying diagnosis was made in 67 % of cases (6/9), with an underlying type of ichthyosis in 44 % (4/9). In two patients, mutations were found in *IL36RN* and *SPINK5*, defining: Deficiency of Interleukin-36 Receptor Antagonist (DITRA) and Netherton syndrome, respectively. In two patients, no pathogenic mutations could be found, and in one patient, a VUS in *C5* was found, which was unlikely to have contributed to the clinical presentation.

The obtained diagnostic yield of 60 % in the prospective group was higher compared to, for instance, NGS panels for other heterogeneous entities like primary immunodeficiencies (33–48 %) [3], hereditary anemias (45.8 %) [4] and monogenic liver diseases (17 %) [5]. This confirms the strong genetic etiology of neonatal erythroderma. Along with the genetic heterogeneity this demonstrates the relevance of performing NGS for NE.

Additionally, our results confirm that a form of ichthyosis is the most likely diagnosis in cases of NE accompanied by a collodion. In contrast, in patients without a collodion membrane, other diagnoses are more likely (OR 6, chi-squared: 0.03). In the patient with DITRA, the diagnosis resulted in a significant therapeutic change later on [6]. Since results are limited to a Dutch population, genetic differences are possible in other populations [7, 8]. A limitation in this study relates to the use of a targeted NGS panel: since causal genes, such as *SULT2B1*, were not known as related to ichthyosis and thus not included during the study, a higher yield in diagnostic outcome in our study population could have been achieved if open exome (WES; Whole Exome Sequencing) analysis had been performed. On the other hand, the patients lacking a genetic diagnosis might not have had a genetic basis for their NE.

In conclusion, this study underscores the relevance of the use of NGS to establish a diagnosis for patients with NE. In the absence of a collodion membrane, causes other than the relatively non-life-threatening ichthyoses, such as

Table 1 Next generation sequencing outcome of (likely) pathogenic mutations in nine prospective (1–9) and eight retrospective (10–17) patients with neonatal erythroderma.

Patient	Collodion	Gene	Variant description	Protein	Status of mutation	Type of mutation	Clinical significance*	Diagnosis (inheritance)
1	Yes	*ABCA12*	NM_173076: c.6091T>G	p.Trp2031Gly	Hom	Missense	Likely pathogenic	HI (AR)
2	Yes	*ALOX12B*	NM_001139.3: c.1463G>A	p.Arg488His	Hom	Missense	Pathogenic	SHCB (AR)
3	Yes	*ALOX12B*	NM_001139: c.1642C>T NM_001139: c.1349G>A	p.Arg548Trp p.Gly450Glu	Het Het	Missense Missense	Pathogenic VUS	LI* (AR)
4	Yes	*ALOX12B*	NM_001139: c..467_470dup NM_001139: c. 1562A>G	p.His158fs p.Tyr521Cys	Het Het	Frameshift Missense	Pathogenic Pathogenic	ARCI (AR)
5	No	*ALOXE3*	NM_001165960.1: c.2285C>T	p.Pro762Leu	Hom	Missense	Pathogenic	ARCI (AR)
6	Yes	*PNPLA1*	NM_173676.2: c.488C>T	p.Pro163Leu	Hom	Missense	Pathogenic	ARCI (AR)
7	Yes	*TGM1*	NM_00359.3: c.877-2A>G	p.(?); (?)	Hom	Splice site	Pathogenic	ARCI (AR)
8	Yes	*TGM1*	NM_00359.3: c.968G>A	p.Arg323Gln	Hom	Missense	Likely pathogenic	SHCB (AR)
9	Yes	*TGM1*	NM_00359.3: c.857G>A; 857G>A	p.Arg286Gln	Hom	Missense	Likely pathogenic	SHCB (AR)
10	No	*ABCA12*	NM_173076: c.6440dup NM_173076.2: c.3180-6T>G	p.Gln2149fs p.(?)	Het Het	Frameshift Splice site	Pathogenic VUS	ARCI* (AR)
11	Yes	*ALDH3A2*	NM_000382.3: c.1297_1298del	p.Glu433fs	Hom	Frameshift	Pathogenic	SLS (AR)
12	Yes	*ALOXE3*	NM_001165960.1: c.1642T>C NM_001165960.1: c.2285C>T	p.Cys548Arg p.Pro762Leu	Het Het	Missense Missense	Likely pathogenic Pathogenic	ARCI (AR)
13	No	*IL36RN*	NM_173170.1: c.80T>C	p.Leu27Pro	Hom	Missense	Pathogenic	DITRA (AR)
14	Yes	*KRT10*	NM_000421.3: c.1468_1473delinsAGTTCCG	p.Gly490fs	Het	Frameshift	Likely pathogenic	Ichthyosis with confetti (AD)
15	No	*SPINK5*	NM_006846.3: c.649C>T NM_006846.3: c.724G>T	p.Arg217 *p.Glu242*	Het Het	Nonsense Nonsense	Likely Pathogenic	NS (AR)
16	Yes	*TGM1*	NM_00359.3: c.1472C>T	p.Thr491Met	Het	Missense	Pathogenic	LI* (AR)
17	No	*DSG1*	NM_001942.2: c.382C>T	p. Arg128*	Het	Nonsense	Pathogenic	SAM* (AR)

Abbr.: AD, autosomal dominant; AR, autosomal recessive; ARCI, autosomal recessive congenital ichthyosis; DITRA, deficiency of interleukin receptor-36 antagonist; Het, Heterozygous; HI, Harlequin ichthyosis; Hom, Homozygous; LI, Lamellar ichthyosis; N/A, Not Available; NGS, Next Generation Sequencing; NS, Netherton syndrome; SAM, severe dermatitis, atopic diathesis and metabolic syndrome; SHCB, self-healing collodion baby; SLS, Sjögren-Larsson syndrome.
*According to AMCG guidelines 2015 [10]; **Clinically conform diagnosis; ***No genetic diagnosis; ****2nd mutation (large deletion) was detected elsewhere, but not with current NGS method.

immunodeficiencies, metabolic disorders or DITRA, are possible. In newborns, these might be detected through genetic evaluations at an earlier stage than onset of clinical signs. Immunodeficiencies such as Omenn syndrome can be present with congenital erythroderma but without typical associated systemic symptoms such as a failure to thrive, infections and fever [9]. These life-threating conditions require immediate and adequate therapy, which can be facilitated by rapid NGS diagnostics. This is now feasible for newborns with NE.

Acknowledgments

The authors thank all parents who gave informed consent for their children. The authors acknowledge all physicians, dermatologists and pediatricians for their efforts and contributions to this study in The Netherlands. This study is part of the Academic Centers of Excellence of Congenital Anatomical Abnormalities and Primary Immunodeficiency Center of the Erasmus MC University Medical Center-Sophia Children's Hospital and of European Reference Network-SKIN-Ichthyosis. The authors are indebted to M. van Geel, MD, PhD, clinical geneticist, Maastricht University Medical Center, the Netherlands, for his contribution in SAM syndrome.

Open access funding enabled and organized by Projekt DEAL.

Funding

The study was funded by Fonds NutsOhra and Stichting Coolsingel.

Conflict of interest

None.

Edwin Cuperus[1,2], Vigfús Sigurdsson[3], Peter C. van den Akker[4], Marieke C. Bolling[5], Mariëlle E. van Gijn[4,6,*], Suzanne G. M. A. Pasmans[1]

(1) Department of Dermatology, Center of Pediatric Dermatology, Erasmus MC University Medical Center Rotterdam-Sophia Children's Hospital, Rotterdam, The Netherlands
(2) Department of Dermatology, St Jansdal Hospital, Harderwijk, The Netherlands
(3) Department of Dermatology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands
(4) Department of Genetics, University Medical Center, University of Groningen, Groningen, The Netherlands
(5) Department of Dermatology, University Medical Center, University of Groningen, Groningen, The Netherlands
(6) Department of Genetics, University Medical Center Utrecht and Wilhelmina's Children Hospital Utrecht, Utrecht, The Netherlands

*The last two authors contributed equally to the present article.

Correspondence to

Suzanne G. M. A. Pasmans, MD, PhD
Department of Dermatology
Erasmus MC-Sophia Children's Hospital
University Medical Centre Rotterdam

Wytemaweg 80
3015 CN Rotterdam, The Netherlands

E-mail: s.pasmans@erasmusmc.nl

References

1 Ott H. Guidance for assessment of erythroderma in neonates and infants for the pediatric immunologist. Pediatr Allergy Immunol 2019; 30(3): 259–68.
2 Pruzskowski A, Bodemer C, Fraitag S et al. Neonatal and infantile erythrodermas. A retrospective study of 51 patients. Arch Dermatol 2000; 136: 875–80.
3 Rae W, Ward D, Mattocks C et al. Clinical efficacy of a next-generation sequencing gene panel for primary immunodeficiency diagnostics. Clin Genet 2018; 93(3): 647–55.
4 Russo R, Andolfo I, Manna F et al. Multi-gene panel testing improves diagnosis and management of patients with hereditary anemias. Am J Hematol 2018; 93(5): 672–82.
5 Stalke A, Skawran B, Auber B et al. Diagnosis of monogenic liver diseases in childhood by next-generation sequencing. Clin Genet 2018; 93(3): 665–70.
6 Cuperus E, Koevoets R, van der Smagt JJ et al. Juvenile interleukin-36 receptor antagonist deficiency (DITRA) with c.80T>C (p.Leu27Pro) mutation successfully treated with etanercept and acitretin. JAAD Case Rep 2018; 4(2): 192–5.
7 El-Sayed N, Seifeldin NS, Gobrial CKT. High frequency of primary hereditary icthyoses in the North-East region of Cairo, Egypt. Postepy Dermatol Alergol 2018; 35(2): 161–6.
8 Youssefian L, Vahidnezhad H, Saeidian AH et al. Autosomal recessive congenital ichthyosis: Genomic landscape and phenotypic spectrum in a cohort of 125 consanguineous families. Human Mutation 2019; 40: 288–98.
9 Cuperus E, van Montfrans JM, van Gijn ME et al. Congenital erythroderma should be considered as an urgent warning sign of immunodeficiency: a case of Omenn syndrome. Eur J Dermatol 2017; 27(3): 313–4.
10 Richards S, Aziz N, Bale S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17(5): 405–24.

