Clinical Rheumatology (2018) 37:1739–1741
https://doi.org/10.1007/s10067-018-4090-6

EDITORIAL

Psoriatic disease treatment nowadays: unmet needs among the "jungle of biologic drugs and small molecules"

Matteo Megna[1] · Anna Balato[2] · Maddalena Napolitano[3] · Lucia Gallo[1] · Francesco Caso[4] · Luisa Costa[4] · Nicola Balato[1] · Raffaele Scarpa[4]

Received: 19 March 2018 / Revised: 24 March 2018 / Accepted: 28 March 2018 / Published online: 11 April 2018

Rheumatology is the branch of medicine dealing with the diagnosis and treatment of articular and connective tissue diseases. Outstanding progresses have been done in the last few decades regarding diseases pathogenesis and new diagnostic processes as well as innovative therapies [1]. Indubitably, the evolution in psoriatic arthritis (PsA) knowledge represents an emblematic example [2]. Indeed, fundamental advances in understanding PsA pathogenesis and natural history have deeply changed its perception by both patients and physicians [3]. In the past, psoriasis was considered just a mere esthetic concern due to a primary defect in keratinocytes, leading to their hyper-proliferation. Nowadays, it is well known that psoriasis and PsA have to be considered a systemic disease, not limited to the skin and joints, but linked to increased cardiovascular risk, obesity, and metabolic syndrome through a shared chronic pro-inflammatory background, establishing the concept of psoriatic disease (PsD) [4]. PsD often requires a multidisciplinary approach through the collaboration of dermatologist, rheumatologist, immunologist, etc. [5]. In addition, being a chronic inflammatory multifactorial disease and dysregulation of immune cells (Th1 and Th17 above all) have been reported as key features of PsD pathogenesis [6]. In this context, a major role is played by inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-17, IL-22, and IL-23 [6, 7]. Advances in PsD pathogenesis have put the basis for the development of new effective drugs for its treatment. Particularly, monoclonal antibody and fusion protein able to inhibit the effects of pro-inflammatory cytokines involved in PsD development, the so-called biologic drugs, have completely revolutionized disease management [8]. It is relevant, for example, that 40 years ago topical treatments such as corticosteroid, salicylic acid, and coal tar represented the main stay of psoriasis therapies, whereas nowadays different new systemic drugs are available such as biologics like anti-TNF-α (adalimumab, etanercept, golimumab, certolizumab, infliximab), anti-IL-12–23 (ustekinumab), and anti-IL-17 (ixekizumab, secukinumab) [8–10]. Moreover, literature is constantly enriching of clinical trials and surveys regarding newer biologic drugs which will be soon available for psoriasis and PsA treatment such as anti-IL-17 receptor (brodalumab) [11], anti-IL-23 (guselkumab, tildrakizumab) [12, 13], and anti-CD6 (itolizumab) [14]. However, PsD treatment scenario is going to become more and more complex and wide apart from the development of biologic drugs. A new era will be introduced by the so-called small molecules which are able to act at the basis of the pro-inflammatory cascade which dominates PsD pathogenesis, preventing the production of inflammatory cytokines. This is the case of molecules such as phosphodiesterase 4 (PDE4) inhibitor (apremilast) and Janus kinase (JAK) inhibitor (tofacitinib) [15].

The intracellular enzyme, PDE4, hydrolyzes cyclic adenosine monophosphate (cAMP) into the intracellular second messenger AMP and activates protein kinase A, leading to regulation of anti-inflammatory and pro-inflammatory cytokines, chemokines, and leukotriene B4 [16].

Further, in PsD, a coordinate involvement of the JAK-STAT phosphoproteins pathway has been found [17]. Apremilast and tofacitinib, targeting respectively PDE4 and JAK molecules, have been showed efficacious on psoriasis and PsA [18–21].

Therefore, insights into the pathogenesis of PsD increasing the understanding of the action of cytokines and their

✉ Raffaele Scarpa
rscarpa@unina.it

[1] Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[2] Department of Advanced Biomedical Sciences, Dermatology Unit, University of Naples Federico II, Naples, Italy

[3] Dipartimento di Medicina e Scienze della Salute "Vincenzo Tiberio", Università degli Studi del Molise, Campobasso, Italy

[4] Rheumatology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

associated transduction pathways have indubitably yielded a number of new therapeutic targets [22, 23].

The introduction of biological agents has changed the way we treat PsD, providing more efficacious and directed therapy for this complex disease. However, PsD is a chronic condition and, therefore, requires long-term management with safe and effective therapy. Although the number of available drugs is continuously growing, there still exist some limitations such as predicting side-effect profile, immunogenicity, and primary lack or secondary loss of efficacy [24]. Indeed, there is a great interest in concepts such as precision medicine [25] and pharmacogenomics [26] in order to find biomarkers which can help and guide the clinician in the treatment choice, predicting higher or lower percentage of efficacy and side effects, also to put the basis for a real tailored and patient-centered therapy. Indeed, head to head studies between different biologic drugs are limited as well as data on how long any treatment should be given and when and how to terminate [27]. These drugs, which present different targets, dosage, and treatment schedules, are used following clinical experience and trials data. However, real-life patients are very different from those enrolled in clinical trials, often presenting comorbidities and/or polypharmacotherapy which can strongly influence biologic treatment outcomes [28, 29]. Moreover, PsD may present different phenotypes apart from the most common form of skin manifestations and articular subsets [30] for which the majority of clinical trials is conducted for. As a result, there is a strict need of fixed rules or shared guidelines which regulate therapy choice between biologics for PsD, highlighting first-line treatments for different patients and their peculiarities (e.g., following different body area involved, being a naïve patient or not, subjects with previous biologic drug failure, comorbidities, articular phenotype, psoriasis subtype, etc.), supporting an algorithm which suggests which drug to choose when a patient with PsD qualifies for systemic therapy. In addition, with a particular regard on cutaneous involvement, many other aspects still remain to be addressed such as treatment goals, adjusting biologics dose and intervals, and the issue of anti-drug antibody.

For all these reasons, the development of new biologic drugs and small molecules for PsD has not only increased the power and the effectiveness of treatment weapons against it but also enhanced the complexity of management strategies creating a "biologic and small molecules jungle" where the clinician can move only following limited evidences and clinical experiences. Hence, a continuous collaborative effort of investigation in order to clarify the complexity of the pathogenetic mechanisms and clinical aspects should be encouraged. This is indubitably the time to develop new surveys, empowering precision medicine and pharmacogenomics strategies, to highlight markers which can guide and help clinician in PsD treatment choice in order to personalize therapy for the right patient in the right time.

Compliance with ethical standards

Disclosures None.

References

1. Napolitano M, Caso F, Scarpa R, Megna M, Patrì A, Balato N, Costa L (2016) Psoriatic arthritis and psoriasis: differential diagnosis. Clin Rheumatol 35:1893–1901
2. Costa L, Caso F, D'Elia L, Atteno M, Peluso R, Del Puente A, Strazzullo P, Scarpa R (2012) Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. Clin Rheumatol 31:711–715
3. Fiocco U, Stramare R, Coran A, Grisan E, Scagliori E, Caso F, Costa L, Lunardi F, Oliviero F, Bianchi FC, Scanu A, Martini V, Boso D, Beltrame V, Vezzù M, Cozzi L, Scarpa R, Sacerdoti D, Punzi L, Doria A, Calabrese F, Rubaltelli L (2015) Vascular perfusion kinetics by contrast-enhanced ultrasound are related to synovial microvascularity in the joints of psoriatic arthritis. Clin Rheumatol 34:1903–1912
4. Caso F, Del Puente A, Oliviero F, Peluso R, Girolimetto N, Bottiglieri P, Foglia F, Benigno C, Tasso M, Punzi L, Scarpa R, Costa L (2018) Metabolic syndrome in psoriatic arthritis: the interplay with cutaneous involvement. Evidences from literature and a recent cross-sectional study. Clin Rheumatol 37:579–586
5. Lapadula G, Marchesoni A, Salaffi F, Ramonda R, Salvarani C, Punzi L, Costa L, Caso F, Simone D, Baiocchi G, Scioscia C, Di Carlo M, Scarpa R, Ferraccioli G (2016) Evidence-based algorithm for diagnosis and assessment in psoriatic arthritis: results by Italian DElphi in psoriatic arthritis (IDEA). Reumatismo 68:126–136
6. Fiocco U, Martini V, Accordi B, Caso F, Costa L, Oliviero F, Scanu A, Facco M, Boso D, Gatto M, Felicetti M, Frallonardo P, Ramonda R, Piva L, Zambello R, Agostini C, Scarpa R, Basso G, Semenzato G, Dayer JM, Punzi L, Doria A (2015) Transcriptional network profile on synovial fluid T cells in psoriatic arthritis. Clin Rheumatol 34:1571–1580
7. Balato A, Schiattarella M, Di Caprio R, Lembo S, Mattii M, Balato N, Ayala F (2014) Effects of adalimumab therapy in adult subjects with moderate-to-severe psoriasis on Th17 pathway. J Eur Acad Dermatol Venereol 28:1016–1024
8. Caso F, Lubrano E, Del Puente A, Caso P, Peluso R, Foglia F, Benigno C, Girolimetto N, Bottiglieri P, Scarpa R, Costa L (2016) Progress in understanding and utilizing TNF-α inhibition for the treatment of psoriatic arthritis. Expert Rev Clin Immunol 12:315–331
9. (1977) The hazardous jungle of topical steroids. Lancet 2:487–8
10. Caso F, Del Puente A, Peluso R, Caso P, Girolimetto N, Del Puente A, Scarpa R, Costa L (2016) Emerging drugs for psoriatic arthritis. Expert Opin Emerg Drugs 21:69–79
11. Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study group (2016) Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase I randomized controlled study. J Dermatol Sci 81:44–52
12. Megna M, Balato A, Raimondo A, Balato N (2018) Guselkumab for the treatment of psoriasis. Expert Opin Biol Ther 18:459–468. https://doi.org/10.1080/14712598.2018.1445223
13. Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, Gottlieb AB, Nakagawa H, Bowman EP, Mehta A, Li Q, Zhou Y, Shames R (2015) Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol 173:930–939

14. Krupashankar DS, Dogra S, Kura M, Saraswat A, Budamakuntla L, Sumathy TK, Shah R, Gopal MG, Narayana Rao T, Srinivas CR, Bhat R, Shetty N, Manmohan G, Sai Krishna K, Padmaja D, Pratap DV, Garg V, Gupta S, Pandey N, Khopkar U, Montero E, Ramakrishnan MS, Nair P, Ganapathi PC (2014) Efficacy and safety of itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, phase-III study. J Am Acad Dermatol 71:484–492
15. Costa L, Del Puente A, Peluso R, Tasso M, Caso P, Chimenti MS, Sabbatino V, Girolimetto N, Benigno C, Bertolini N, Del Puente A, Perricone R, Scarpa R, Caso F (2017) Small molecule therapy for managing moderate to severe psoriatic arthritis. Expert Opin Pharmacother 18:1557–1567
16. Castro A, Jerez MJ, Gil C, Martinez A (2005) Cyclic nucleotide phosphodiesterases and their role in immunomodulatory responses: advances in the development of specific phosphodiesterase inhibitors. Med Res Rev 25:229–244
17. Fiocco U, Accordi B, Martini V, Oliviero F, Facco M, Cabrelle A, Piva L, Molena B, Caso F, Costa L, Scanu A, Pagnin E, Atteno M, Scarpa R, Basso G, Semenzato G, Punzi L, Doria A, Dayer JM (2014) JAK/STAT/PKCδ molecular pathways in synovial fluid T lymphocytes reflect the in vivo T helper-17 expansion in psoriatic arthritis. Immunol Res 58:61–69
18. Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, Crowley J (2016) Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol 74:134–142
19. Schett G, Wollenhaupt J, Papp K, Joos R, Rodrigues JF, Vessey AR, Hu C, Stevens R, de Vlam KL (2012) Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 64: 3156–3167
20. Krueger J, Clark JD, Suárez-Fariñas M, Fuentes-Duculan J, Cueto I, Wang CQ, Tan H, Wolk R, Rottinghaus ST, Whitley MZ, Valdez H, von Schack D, O'Neil SP, Reddy PS, Tatulych S, A3921147 Study I (2016) Tofacitinib attenuates pathologic immune pathways in patients with psoriasis: a randomized phase 2 study. J Allergy Clin Immunol 137:1079–1090
21. Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, Kudlacz E, Wang C, Menon S, Hendrikx T, Kanik KS (2017) Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 377:1525–1536
22. Scarpa R, Caso F, Costa L, Peluso R, Del Puente A, Olivieri I (2017) Psoriatic disease 10 years later. J Rheumatol 44:1298–1301
23. Cafaro G, McInnes IB (2018) Psoriatic arthritis: tissue-directed inflammation? Clin Rheumatol. https://doi.org/10.1007/s10067-018-4012-7
24. Costa L, Perricone C, Chimenti MS, Del Puente A, Caso P, Peluso R, Bottiglieri P, Scarpa R, Caso F (2017) Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D 17:509–522
25. Alwan W, Nestle FO (2015) Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine. Clin Exp Rheumatol 33:S2–S6
26. Foulkes AC, Warren RB (2015) Pharmacogenomics and the resulting impact on psoriasis therapies. Dermatol Clin 33:149–160
27. Mrowietz U, Steinz K, Gerdes S (2014) Psoriasis: to treat or to manage? Exp Dermatol 23:705–709
28. Scarpa R, Caso F (2018) Spondyloarthritis: which composite measures to use in psoriatic arthritis? Nat Rev Rheumatol 14:125–126
29. Costa L, Caso F, Atteno M, Del Puente A, Darda MA, Caso P, Ortolan A, Fiocco U, Ramonda R, Punzi L, Scarpa R (2014) Impact of 24-month treatment with etanercept, adalimumab, or methotrexate on metabolic syndrome components in a cohort of 210 psoriatic arthritis patients. Clin Rheumatol 33:833–839
30. Caso F, Costa L, Atteno M, Del Puente A, Cantarini L, Lubrano E, Scarpa R (2014) Simple clinical indicators for early psoriatic arthritis detection. Springerplus 3:759