IL-1 Inhibition in Cryopyrin-Associated Periodic Syndrome and Beyond: A Million Dollar Question about the Injection Schedule of Biotherapies

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In this issue of *Dermatology*, our colleagues from Basel raise an important issue: the timing of injections of canakinumab in patients with cryopyrin-associated periodic syndrome (CAPS) [1]. Beyond specific diseases such as CAPS, this question is relevant to the way we use biotherapies in inflammatory disorders. Medications are approved according to the results of clinical trials, which were designed by pharmaceutical companies. Officially recommended and approved dosages and administration schedules are therefore those that were used in the trials. At the moment of commercialization, they are the only evidence-based data, but they are not necessarily the best administration schedule/dosage for the patients, or for the health care insurance. In the case of the numerous biotherapies currently available, the optimal dosing and timing of injections is of uttermost importance. First, many of these drugs are immunosuppressors or immunomodulators and there should definitely be concern about long-term tolerance and risks, and thus the lowest efficient dosage should intuitively be the best. Second, the price of these drugs is often exceedingly high, as for example the annual cost of canakinumab which is about 88,500 Euros! For instance, the switch of anakinra to canakinumab in patient 2, who was controlled with the former treatment and who tolerated it well, bears a cost of more than 70,000 Euros/year.

Mueller et al. [1] showed that re-dosing with canakinumab on relapse ('reflare-guided drug schedule') rather than dosing every 8 weeks as officially recommended allowed control of the disease but reduced the drug consumption by 50%. The treatment remained effective, indeed it was possible to reduce the dose by further 50% in the second patient. This approach seems logical, safe with regard to potential drug toxicity as cumulative exposure is reduced, and less economically wasteful. Potential concerns about the risk of developing AA amyloidosis compared to 'standard' dosing, i.e. the doses used in the pivotal study, are theoretical and can be circumvented by regular measurement of SAA serum levels. Another option would be pharmacologic monitoring; the risk of a CAPS flare is thought to be less than 1% at canakinumab levels of 1 µg/ml. In patient 2 serum level of this drug was 1.523 µg/ml at week 12, though it was administered at only half of the recommended dosage. Though drug monitoring and pharmacogenics are potential approaches that would initially increase the cost of very expensive treatments, they might eventually allow economies by facilitating individually tailored dosing, as is suggested by the example of infliximab, a TNF-inhibitor, in rheumatoid arthritis [2]. Nevertheless, in the field of psoriasis, efficiency and cost-effectiveness studies are usually based on the clas-

Table 1. IL-1 inhibitors

Drug	Mechanism	Half-life	Official indication	Recommended administration scheme
Anakinra (Kineret®)	IL-1 receptor antagonist	4 to 6 h	Rheumatoid arthritis (in association with methotrexate)	daily
Rilonacept (Arcalyst®)	Dimeric protein which acts as a soluble receptor and 'traps' IL-1	6 to 7 days	CAPS	weekly
Canakinumab (Ilaris®)	Anti-IL-1 antibody	26 days	CAPS	every 8 weeks
Gevokizumab (Xoma 052)	Anti-IL-1 antibody	23 days	Clinical studies still ongoing; especially in CAPS, Behcet's disease, type II Diabetes	

Table 2. Some neutrophilic dermatoses responsive to IL-1 inhibition and monogenic and complex disorders in which they can occur

Dermatological sign with tissular neutrophilic infiltration (nosologic entity)	Hereditary auto-inflammatory syndrome	Related sporadic or complex disorder
Evanescant maculo-papular rash (nosology = neutrophilic urticarial dermatosis)	CAPS	Schnitzler syndrome Adult-onset Still disease Systemic juvenile arthritis
Ulceration (nosology = pyoderma gangrenosum)	PAPA	Pyoderma gangrenosum 'idiopathic' or occurring in the setting of a nosologically characterized inflammatory disease
Pustule (asptic)	DIRA PAPA	Generalized pustular psoriasis Impetigo herpetiformis SAPHO syndrome Acne fulminans
Edematous plaque (nosology = Sweet syndrome)	Majeed syndrome	Sweet syndrome either 'idiopathic' or occurring in the setting of a nosologically characterized inflammatory disease

DIRA = Deficiency of interleukin-1 receptor antagonist; PAPA = pyogenic arthritis, pyoderma gangrenosum and acne.

sic administration schedules [3–5], though registries [6] would probably allow an analysis of 'reflare-guided drug schedules'.

To find the best and most economic treatment strategy of each biologic in every disease we use it is an important task for the coming years. Governments and health care insurances should support such studies, since they will probably allow substantial economies.

The CAPS are a paradigm of auto-inflammatory disorders and they are nicely described in the introduction of the paper by Mueller et al. [1]. CAPS are currently the only approved indication of canakinumab. The authors have confirmed the spectacular efficiency of both IL-1 inhibitors, anakinra and canakinumab, in this indica-

tion. It is also worth highlighting that these agents have a reassuring safety profile to date and appear effective as monotherapy. In addition, unlike many of the therapeutics used in systemic inflammatory diseases there is no need to provide additional drugs to control treatment-related side effects. Up to now, paradoxal aggravations, as described with anti-TNF drugs for example [7], are not reported.

There are other potential indications of IL-1 inhibitors in dermatology. There are currently 4 different IL-1 inhibitors, summarized in table 1, of which 2 are available in most European countries. Anakinra is the most widely used and prescribed of them. Though this drug is approved only for patients with rheumatoid arthritis in as-

sociation with methotrexate, the drug has shown very promising results in many other diseases which are relevant to the dermatologist including other rare auto-inflammatory disorders such as DIRA (deficiency of the interleukin-1 receptor antagonist) syndrome, TRAPS (TNF-receptor-associated periodic syndrome), mevalonate kinase deficiency and colchicine-resistant familial Mediterranean fever, to name but a few [8–11]. Analysis of the literature and our own experience show that IL-1 inhibition seems a very interesting treatment option in many acute neutrophilic dermatoses, especially when fever and leucocytosis are present [12–15]; many of those neutrophilic dermatoses are also disease expressions of authentic monogenic auto-inflammatory disorders. Some examples are summarized in table 2. Thus, in patients with supposed auto-inflammatory mechanism, IL-1 inhibitors are a logical treatment as an increase in IL-1 release by monocyte-macrophage is probably the key pathogenetic mechanism; anti-TNF drugs were also successfully used in some patients [16, 17].

Interestingly, IL-1 antagonists do not seem effective in neutrophilic dermatoses with a more chronic or protracted course like erythema elevatum diutinum (D. Lipsker, personal observation). Currently, their usage in neutrophilic dermatoses should of course be restricted to cases in which conventional therapies have failed or are contraindicated. Furthermore, we completely share the point of view of Mueller et al. [1] and think that 'reflare-guided' treatment courses are probably adequate in many, though probably not all, of these diseases or patients. Clearly, this class of drugs is a new treatment option for some inflammatory diseases; it is especially relevant to those with an underlying auto-inflammatory mechanism and we tried to classify some of the inflammatory diseases according to the predominant auto-immune or auto-inflammatory disease mechanism in a previous editorial in this journal [18]. As dermatologists are confronted to many diseases with supposed underlying auto-inflammatory pathogenesis, namely the neutrophilic dermatoses, they should pay attention to this new class of biologics.

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