Review Article

Review on Novel Drugs for Gout

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ABSTRACT

Gout is a kind of arthritis which is caused by the accumulation of monosodium uric acid crystals especially in joints. 8.3 million People in the United States are affected with gout and Prevalence is approximately 20% in patients with a family history of gout. Controlling the acute flares has been the first priority in the management of gout. As there are limitations in approved therapies for gout especially with patients who frequently have multiple comorbidities. Because of the greater understanding of the pathophysiology of gout, it has resulted in the discovery of new therapies to treat and prevent gout flares and underlying hyperuricemia. Novel therapies will lower serum urate levels or treat and prevent acute gouty flares. This review describes various novel drugs for treating the gout and their safety and efficacy when compared to other traditional drugs used for gout.

Keywords: Gout, Hyperuricemia, Anakinra, Canakinumab, Adrenocorticotropic hormone, Caspase inhibitors.

INTRODUCTION

Gout is the most common type of inflammatory arthritis in adults that occurs due to elevated serum urate levels resulting in deposition of monosodium urate (MSU) crystals in articular and periarticular tissues.[1] If serum uric acid level exceeds 6.8 mg/dl, it is termed as hyperuricemia. The prevalence of gout in the USA is 3.9 % which means 8.3 million adults are affected with gout whereas the prevalence of hyperuricemia in USA is 21.4 % or about 43.3 million individuals are affected.[2] Worldwide incidence of gout has been increased gradually due to poor dietary habits such as fast foods, lack of exercises, increased incidence of obesity and metabolic syndrome.[3]In spite of rise in prevalence, the current therapy for gout is often limited because of its side effects, various comorbidities such as such as cardiovascular disease, diabetes mellitus, hypertension, chronic kidney disease, metabolic syndrome) and drug-drug interactions.[4] Though the pathophysiology of hyperuricemia (HU) and gout is well understood, its management still remains remarkably suboptimal, leading to frequent recurrent flares, increased hospitalization rates in the US, and worsening economic burden.[3,5] Conventionally, lowering serum urate levels via inhibiting uric acid synthesis (de novo) has been the preferred approach with xanthine oxidase inhibitors such as allopurinol and febuxostat.[6] The better understanding of pathogenesis of gout over the past few decades provided the impetus for new, more specific therapeutic targets. This review describes all most all the new drugs for the treating inflammation in acute gout, including biologics such as Anakinra, Canakinumab, and Rilonacept. Apart from this, other anti-inflammatory agents such as Corticotrophin and Melanocortins and Caspase inhibitors may be on the horizon for prophylaxis and treatment of acute gout flares. Additionally, the drugs like Benzbromarone, Arhalofenate, Lesinurad, Tranilast, Levotofisopam, Verinurad and Purine nucleoside phosphorylase inhibitor like Ulodesine are included in this review.

Anakinra

Anakinra is a recombinant human IL-1β receptor antagonist which has been approved by US FDA for rheumatoid arthritis and neonatal-onset multi-system inflammatory disease. To date, randomized controlled trials assessing anakinra's efficacy in the management of gout flares are still lacking[7], but there are some case series and uncontrolled trials which are supporting its efficacy in treating gout flares.[8,9] In practice, Anakinra is preferred off-label anti-IL-1β strategy among experienced "goutologists", based on its relative short half-life and lower cost when compared to Canakinumab.

Canakinumab

Canakinumab is a completely humanized anti-IL-1βmonoclonal antibody which binds to soluble IL-1β and thereby prevents receptor activation.[10, 11]US Food and Drug Administration (FDA) approved Canakinumab for cryopyrin-associated periodic fever syndromes, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, and systemic idiopathic juvenile arthritis.[12]In One double-blind study assessment of efficacy and safety of one dose of 150 mg Canakinumab against one single dose of triamcinolone injection at baseline and also during an acute gout attack in patients frequently flaring with contraindications to use of NSAIDs and/or colchicine has been performed.[13] This study proved Canakinumab is having a rapid onset in pain relief and increased the time between a flare, which is likely attributabletoitshalf-lifeof21–28days.[13, 14]Moreadverseeventswere observed in the Canakinumab group, which includes infections, neutropenia, and thrombocytopenia.[13] In another

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comparative study, Canakinumab (single dose versus four divided doses weekly) versus colchicine 0.5 mg daily for gout prophylaxis during initiation of Urate Lowering Therapy (ULT) with allopurinol.[12]In this study, Canakinumab was found to be superior prophylaxis than its comparator colchicine. The use of Canakinumab has been approved by European Medicines Agency for patients with contraindications to use of conventional anti-inflammatory medications.[11]

Rilonacept

Rilonacept is a dimeric fusion protein (or IL-1 Trap) which consists of the extracellular domains of human IL-1β receptor and IL-1 receptor accessory protein which is fused to the Fc portion of human IgG.[10] In a phase 2 trial of Rilonacept (320 mg loading dose and 160 mg weekly) was compared to placebo for prophylaxis while initiating ULT with allopurinol and it was found to be superior in reducing gout flares during this period.[15] Other phase 3 trials have compared Rilonacept versus placebo and the results were found to be similar.[15, 16]Conversely, in a randomized, controlled clinical trial using indomethacin was used as comparator to Rilonacept. In this study, Rilonacept alone or combined with indomethacin was not significantly superior to indomethacin monotherapy.[17]Rilonacept has half-life of 9 days and it was overall well tolerated in both studies with adverse reactions observed were pre-dominantly injection site reactions.[17, 18]

Adrenocorticotropic hormone (ACTH) or corticotropin

Adrenocorticotropic hormone (ACTH) or corticotropin was the first steroid agent which is used in rheumatic disease and its effectiveness as an anti-inflammatory was due to its ability to stimulate adrenal production of corticosterone.[19] ACTH is a precursor molecule for melanocortin, and recently it has been identified that ACTH binds to all five melanocortin receptors besides melanocortin-2 receptor which is responsible for adrenal stimulation. In the management of gout, ACTH acts at melanocortin-3 receptor (MC3R), a member of 7-transmembrane G-protein coupled receptors family.[11, 19] When melanocortin or corticotrophin bounds to MC3R, it initiates anti-inflammatory signals and sequestering the activities of NF-κB and hemeoxygenase, which results in decreased inflammatory cytokine transcription and production.[11] Getting and coworkers further explored this pathway by using a rat model for acute gout.[20, 21]After injection of corticotrophin subcutaneously, rise in levels of corticosterone and signs of reduced inflammation were observed. It was also observed that upon injection of corticotrophin directly into the joint, increased levels of corticosterone were not seen in the setting of decreased inflammation, which indicates that ACTH might have anti-inflammatory properties independent of glucocorticoid release.[20,21]In A case series review of 181 inpatient cases of gout patients was performed in which ACTH was used as first line treatment.[22] Investigators observed that 77 % of patients has shown response after one intramuscular injection. Among remaining non-responders, 87 % received a second injection the following day, of which 82 % were responded[22]. Further clinical trials are needed to evaluate the efficacy of this treatment, as it would fill a critical need for therapies inpatients who are having contraindications to NSAIDs, colchicine, and high-dose oral corticosteroids.

Caspase inhibitors

Caspases-1-4 is involved in inflammasomes and mediates the maturation and secretion of IL-1β.[23]in murine models Caspase inhibitors has shown to inhibit IL-1, but only Case reports are currently available regarding its efficacy in humans.[11]further investigations are needed for evaluating efficacy of caspase inhibitors in treating gout.

Benzbromarone

Benzbromarone is a potent uricosuric agent and it acts by inhibiting URAT 1 (urate transporter) and GLUT 9 (glucose transporter). Benzbromarone has shown to be more potent than probenecid when used as an add-on to 300 daily mg of allopurinol and 92% of participants reached a target SU of 5 mg/dl.[24] Two different comparative studies have compared Benzbromarone to allopurinol showed higher potency of Benzbromarone when compared to the standard dose (300 mg) of allopurinol, but almost equal effectiveness exists after up-titration of allopurinol.[25, 26] In a meta-analysis review, they concluded that there is no significant difference in urate lowering potency and the same review concluded that Benzbromarone is more potent than probenecid in achieving SU goals.[27]

Even In patients with estimated GFR of 20 ml/min Efficacy of Benzbromarone has been seen.[28] Despite of its high efficacy, Benzbromarone was withdrawn from the market in several countries because of post marketing reports of abnormal liver function and deaths from hepatic failure. This risk was especially high in those patients taking high doses of 300 mg daily.[29]interestingly; the systematic review by Kyddet al. concluded that when compared with probenecid, Benzbromarone has fewer withdrawals due to adverse events (AE) and fewer incidence of adverse events.[27]

Arhalofenate

Arhalofenate has dual mechanism of action whose main uricosuric effect comes from the selective inhibition of URAT1 and OAT4. It is also a peroxisome proliferator-activated receptor-ligand (PPAR)-γ partial agonist, and through this mechanism, it reduces IL-1β levels with a potential added benefit of reducing gout flares.[30]it was initially developed to treat diabetes, later it was discovered to have properties advantageous to the treatment of acute and chronic gout.[11, 14]

In an analysis of four global double blinded phase II randomized controlled trials (RCTs) including 955 patients analyzed the effect of different doses of Arhalofenate on SU, there is Statistical significant dose-dependent reductions from baseline SU were in 13%, 22%, and 29% of the patients receiving Arhalofenate 200, 400, and 600 daily

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mg respectively. Upon analyzing patients who have baseline SU was above 6 mg/dl, 48%, 78%, and 83% of patients receiving 200, 400, and 600 mg of Arhalofenate achieved a SU below 6 mg/dl when compared to only 25% in the placebo group and the safety profile was overall good, significant reductions were observed in fasting glucose, hemoglobin A1c and triglycerides were seen in all treatment arms. Another phase II trial was designed for evaluation of arhalofenate's urate lowering effect, and also evaluating its ability to prevent flares. In This 12-week RCT, Arhalofenate has been used in 600 or 800 mg daily doses, when compared to placebo, allopurinol 300 mg daily, and allopurinol 300 mg daily in combination with colchicine 0.6 mg daily.[31] Participants receiving the Arhalofenate 800 mg dose presented with a flare rate reduction of 46% and it is 41% for allopurinol monotherapy and the mean percentage change in SU was 12% and 16% in the Arhalofenate 600 and 800 mg when compared to placebo and there is no statistically significant number of participants reaching a target Serum Uric Acid (SU) of less than 6 mg/dl.

Lesinurad

Lesinurad is a Uric acid Reabsorption inhibitor (URI) and OAT4 inhibitor that inhibits urate transporter-1 (URAT1) in renal tubules, and therefore normalizes uric acid excretion and reduces serum uric acid (sUA) levels.[32]In a recently published multi-center open label trial investigating the efficacy and safety of Lesinurad in combination with febuxostat in 20 subjects, Individuals with baselines UA >8mg/dL were assigned to two groups, febuxostat 40 or 80 mg. Urate levels were checked after administering febuxostat alone for 1 week and in the second week, Lesinurad 400 mg/day was added for 1 week and then increased to 600 mg/day the following week. The results shown that there was a significant decrease in sUA with once daily administration of Lesinurad 400mg in combination with either febuxostat 40 or80 mg/day rather than single dose febuxostat 40or 80 mg/day.[32]

Tranilast

Tranilast was initially developed as medication for asthma and other allergic conditions in Japan, which was shown to reduce SU levels in healthy volunteers. It inhibits GLUT9 and URAT1 transporters and promotes renal excretion of urate.[33] Two phase II clinical trials evaluated the effect of Tranilast, one by using a single dose of Tranilast with various doses ranging from 100 to 900 mg, and the second study has done by using total daily doses of 300, 600 or 900 mg daily during 7 days.[34] In first study mean SU decrease of 0.17 and 0.24 mg/ dl was observed at 4 and 24 hours, respectively and in the second study the mean SU reduced to 1.1, 3.2 and 3.3 mg/dl in 300, 600 and 900 mg groups, respectively. Tranilast also acts as anti-inflammatory which reduces inflammation induced by monosodium urate (MSU) crystals in vivo, by suppressing leukocyte infiltration and plasma extravasation in a similar way to colchicine and indomethacin.[35] This represents an added benefit to ULT therapy with the possibility of flare prevention.

Levotofisopam

Levotofisopam is the S-enantiomer of the racemic mixture tofisopam which is approved in several countries outside the US for the management of a variety of disorders associated with stress or autonomic instability and was found to have uricosuric properties. In a phase II trial with 13 patients with hyperuricemia and gout, one day of Levotofisopam 500 mg daily followed by TID doses and one final single dose on day 7 showed a reduction in mean absolute SU of 3.9 mg/dl (range 2.3–5.3). No significant AEs were reported.

Verinurad

Verinurad is a URAT1 inhibitor which is three times more potent that Benzbromarone and 100 times more potent than probenecid.[37] In a phase I trial, a 36-hour sustained decrease of 60% in SU concentrations was reported in healthy individuals after receiving a single dose of Verinurad 40 mg.[38] Currently, phase II trials comparing monotherapy and combination therapy of allopurinol and febuxostat are ongoing and no results are available at the moment.

Ulodesine

Ulodesine is a purine nucleoside phosphorylase (PNP) inhibitor and It acts upstream of xanthine oxidase in the purine metabolism pathway to reduce serum urate production[39]. In phase 2 placebo-controlled trials, Ulodesine of doses ranging from 40 to 80 mg once daily reduced the sUA levels in conjunction with allopurinol in patients who have not r alone to allopurinol 300mg daily.[40]Another phase 2trial tested the addition of low-dose Ulodesine to various doses of allopurinol. It was observed that 100 % of subjects taking Ulodesine40 and 80 mg/day by combining with 300 mg/day of allopurinol achieved the target of serum uric acid less than 6.0 mg/Dl[11], but the higher doses resulted in more diarrhea and rashes when compared to the placebo group. No increase in infection was observed, which would be a concern, since inborn error of purine metabolism from PNP deficiency is associated with a combined immunodeficiency.[11] further studies have to be done, to find the Ulodesine role in lowering serum uric acid.

CONCLUSION

This review describes about the latest drugs for treating the gout flares and the drugs which are under investigation.

REFERENCES

1. Perez-Ruiz F, Liote F, Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? Arthritis Rheumatology, 57(7), 2007, 1324–8.
2. Zhu Y, Pandya BJ, Choi HK, Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

2007–2008, Arthritis Rheumatology,63(10), 2011, 3136–41.

3. Kuo C.F, Grainge M.J, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors, Natural Review of Rheumatology, 11(11), 2015, 649–662.

4. Keenan RT, O'Brien WR, Lee KH, Crittenden DB, Fisher MC, Goldfarb DS, Krasnokutsky S, Oh C, Pillinger MH, Prevalence of contraindications and prescription of pharmacologic therapies for gout, The American Journal of Medicine, 124(2), 2011, 155–63.

5. Lim SY, Lu N, Fisher M, Oza A, Rai SK, Menendez ME, Choi HK, Hospitalization trends of rheumatoid arthritis and gout in the United States, The journal of the American Medical Association, 315(21), 2016, 2345-7.

6. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J, Gout-associated uric acid crystals activate the NALP3 Inflammasome, Nature, 440(7081), 2006, 237–41.

7. Dinesh Khanna, John D. FitzGerald, Puja P. Khanna, SangmeeBae, Manjit Singh, TuhinaNeogi, Michael H. Pillinger, Joan Merill, Susan Lee, Shraddha Prakash, Marian Kaldas, ManeeshGogia, Fernando Perez-Ruiz, Will Taylor, FrédéricLioté, Hyon Choi, Jasvinder A. Singh, Nicola Dalbeth, Sanford Kaplan, Vandana Niyyar, Danielle Jones, Steven A. Yarows, Blake Roessler, Gail Kerr, Charles King, Gerald Levy, Daniel E. Furst, N. Lawrence Edwards, Brian Mandell, H. Ralph Schumacher, Mark Robbins, Neil Wenger and Robert Terkeltaub, 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care &Research, 64(10), 2012, 1447–61.

8. So A, De Smedt T, Revaz S, Tschopp J, A pilot study of IL-1 inhibition by Anakinra in acute gout, Arthritis Research & Therapy, 9(2), 2007, R28.

9. Ottaviani S, Moltó A, and Ea. HK, Neveu S, Gill G, Brunier L, Palazzo E, Meyer O, Richette P, Bardin T, Allanore Y, Lioté F, Dougados M, Dieudé P, Efficacy of Anakinra in gouty arthritis: a retrospective study of 40 cases. Arthritis Research & Therapy, 15(5), 2013, R123.

10. Crittenden DB, Pillinger MH, New therapies for gout. Annual Review of Medicine, 64, 2013, 325–37.

11. Edwards NL, SoA, Emerging therapies for gout, Rheumatic Disease Clinics of North America, 40(2), 2014, 375–87.

12. Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, Balfour A, Krammer G, Sallstig P, So A, Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomized study, Annals of Rheumatic Disease, 70(71), 2011, 1264–71.

13. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, Murphy V, Richard D, So AK, Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomized, multicenter, active controlled, double-blind trials and their initial extensions , Annals of Rheumatic Disease, 71(11), 2012, 1839–48.

14. Saha GC, Karpf D, Choi YJ, and Roberts BK. Arhalofenate, a potential novel treatment for hyperuricemia, with or without metabolic co-morbidities, in patients with gout: meta-analysis of urate lowering in four phase 2 studies in type 2 diabetes. Arthritis Rheumatology, 63(10), 2011, 2584.

15. Schumacher HR Jr, Sundy JS, Terkeltaub R, Knapp HR, Mellis SJ, Stahl N, Yancopoulos GD, Soo Y, King-Davis S, Weinstein SP, Radin AR, Rilonacept (interleukin-1trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, placebo-controlled trial, Arthritis Rheumatology, 64(3), 2012, 876–84.

16. Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, Wang J, King-Davis S, Evans RR, Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial, Rheumatology,52(7), 2013, 1285–92.

17. Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, King-Davis S, Weinstein SP, Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator, Arthritis Research & Therapy, 15(1), 2013, R25

18. Schumacher Jr HR, Evans RR, Saag KG, Clower J, Jennings W, Weinstein SP, Yancopoulos GD, Wang J, Terkeltaub R, Rilonacept (interleukin-1trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study, Arthritis Care &Research, 64(10), 2012, 1462–70.

19. Pillinger MH, Keenan RT, Update on the management of hyperuricemia and gout, Bulletin of the NYU Hospital for Joint Diseases, 66(3), 2008, 231–9.

20. Getting SJ, Christian HC, Flower RJ, and Perretti M, Activation of melanocortin type 3 receptor as a molecular mechanism for adrenocorticotropic hormone efficacy in gouty arthritis, Arthritis Rheumatology, 46(10), 2002, 2765–75.

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21. Getting SJ, Lam CW, Chen AS, Grieco P, Perretti M, Melanocortin 3 receptors control crystal-induced inflammation, FASEB Journal, 20(13), 2006, 2234–41.

22. Daoussis D, Antonopoulos I, Yiannopoulos G, Andonopoulos AP, ACTH as first line treatment for acute gout in 181 hospitalized patients, Joint Bone Spine, 80(3), 2013, 291–4.

23. Gross O, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. Inflammasome activators induce interleukin-1alpha secretion via distinct pathways with differential requirement for the protease function of caspase-1, Immunity, 36(3), 2012, 388–400.

24. Reinders M, Van Roon E, Houtman P, Brouwers J and Jansen T, Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously Benzbromarone-treated gout patients, Clinical rheumatology, 26(9), 2007, 1459-6

25. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, Garcia-Erauskin G and Ruiz-Lucea E, Efficacy of allopurinol and Benzbromarone for the control of hyperuricemia, A pathogenic approach to the treatment of primary chronic gout. Annals of Rheumatic Disease, 57, 1998, 545–549.

26. Reinders M, Haagsma, C, Jansen T, Van Roon E, Delsing J, Van De Laar M. A, Brouwers JR, Randomized controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout, Annals of Rheumatic Disease, 68, 2009, 892–897.

27. Kydd A, Seth R, Buchbinder, R, Edwards C, and Bombardier, C. Uricosuric medications for chronic gout. Cochrane Database Systematic Review, 11, 2014, CD010457.

28. Lee M, Graham G, Williams K and Day R. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? Drug Safety, 31, 2008, 643–665.

29. Hautekeete M, Henrion J, Naegels S, Deneve A, Adler M, Deprez C, Severe hepatotoxicity related to benzarone: a report of three cases with two fatalities. Liver, 15, 1995, 25–29.

30. Choi H, Mount D and Reginato A. Pathogenesis of gout, Annals of Internal Medicine, 143, 2005, 499–516.

31. Steinberg A, Chera H, Choi Y, Martin R, Mcwherter C, Zhang Y, A study to evaluate the efficacy and safety of Arhalofenate for preventing flares and reducing serum uric acid in gout patients, Arthritis Rheumatology, 67(10) 2015.

32. Fleischmann R, Roy Fleischmann, Bradley Kerr, Li-Tain Yeh, Matt Suster, Zancong Shen, Elizabeth Polvent, Vijay Hingorani, Barry Quart, Kimberly Manhard, Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of Lesinurad and febuxostat in gout patients with hyperuricaemia. Rheumatology, 53(12), 2014, 2167–74.

33. Mandal A, Emerling D, Serafini T and Mount D. Tranilast Inhibits urate transport medicated by URAT1 and GLUT9, Arthritis Rheumatology, 62, 2010, 164.

34. Sundy J and Kitt M. Tranilast, a novel, potential treatment for the chronic management of hyperuricemia in patients with gout, reduces serum uric acid in healthy subjects, Annals of Rheumatic Diseases, 69, 2010, 607.

35. Serafini T and Emerling D, Tranilast suppresses inflammation induced by monosodium urate crystals in vivo. Annals of Rheumatic Diseases, 69, 2010, 664.

36. Noveck R, Wang Z, Forsthoefel A, Sigmon K, Hall P and Keogh J. Levotofisopam has uricosuric activity and reduces serum urate levels in patients with gout, Arthritis Rheumatology, 64, 2012, 818

37. Miner J and Tan P, RDEA3170, a novel, high affinity URAT1 inhibitor binds to a central domain within URAT1. Annals of Rheumatic Diseases, 71, 2013, 446.

38. Ardea Biosciences Ardea's next-Generation Urat1 Inhibitor, Shows Promising Phase 1 Clinical Results, vol. 2015.

39. Fitz-Patrick DDW, Pappas J, Hollister A, Effects of a purine nucleoside phosphorylase inhibitor, BCX4208, on the serum uric acid concentrations in patients with gout. Arthritis Rheumatology, 62(10), 2010, 150.

40. Hollister AS, Becker MA, Terkeltaub R, Waugh A, Lyman S, Flynt A. BCX4208 synergistically lowers serum uric acid (sUA) levels when combined with allopurinol in patients with gout: results of a phase 2 dose-ranging trial. Arthritis Rheumatology, 63(10), 2011, 1018.

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